Swedish National Institute
of **Public Health**

Adverse Health Consequences of Cannabis Use

A survey of scientific studies
published up to and including 2008

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Foreword

INFORMATION AND PROPAGANDA CONCERNING CANNABIS IS INCREASINGLY spread over the Internet and other media, primarily aimed at young people. National and international interest groups are lobbying for the legalisation of its use. Although research concerning cannabis has increased significantly in recent years, considerable uncertainty still exists in various groups in society regarding the risks associated with cannabis use.

In light of this, the Swedish National Institute of Public Health finds this an appropriate time to summarise the current state of knowledge with regard to the harmful effects of cannabis, which can be found in this report. Results from scientific studies published up to and including 2008 are included. This knowledge overview shows that cannabis use is associated with a number of harmful risks; among the most serious are diminished learning ability and decreased intellectual capacity. Cannabis can also cause serious mental disorders such as schizophrenia and other psychosis. Teenagers are particularly vulnerable and damage can occur even with very moderate consumption. The panorama of harm indicates that it is misleading to view cannabis as a "light" narcotic substance.

This report is an update of *Adverse Health Consequences of Cannabis Use* published by the Swedish National Institute of Public Health in 2004. That report was preceded by a publication under the same title issued by the National Board of Health and Welfare in 1997. The author of all three reports is Jan Ramström, psychiatrist and expert in the field of narcotics. Like the two previous reports, the author is responsible for the interpretations and conclusions presented in this text.

This report is intended for healthcare providers and information officers, as well as interested members of the public who are in need of knowledge-based information on the consequences of cannabis use.

Sarah Wamala
Director-General
Swedish National Institute of Public Health

Introduction

IN 1996, ON BEHALF OF THE SWEDISH NATIONAL BOARD OF HEALTH AND WELFARE, I compiled the report *Skador av hasch och marijuana: En genomgång av vetenskapliga studier av skadepanoramat hos cannabis* (subsequently translated into English as Adverse Health Consequences of Cannabis Use: A Survey of Scientific Studies into the Range of Damage to Health Caused by Cannabis). In the report, I tried to cover all that had been published up to and including February 1996. In 2003, on behalf of the Swedish National Institute of Public Health, the report was updated with the scientific studies published up to and including the autumn of 2003. As with its predecessor, an English version of the report was also published. It was also made available for download from the institute website. The present version has the same structure as the two previous versions. In other words, the additions are not intended to form a supplement, but to be integrated with the earlier material.

Otherwise, this is still a report solely concerning the harmful effects of cannabis use. This is the reason that the introductory remarks on cannabis are so brief.

Trends over the past five-year period

The number of scientific studies about cannabis has increased strongly in the 2000s and publications appear to continue at the same or a higher pace. This is a pleasing trend, although occasionally problematic for the survey author.

There are many reasons for this high level of activity. One reason is the incentive that the "mapping" of the *endocannabinoid system* has entailed. It has entailed an increased understanding of how the exogenous cannabinoids work. Another reason that has certainly been of some significance is the growing interest in the cannabinoids as pharmacons, particularly in the U.S. Researchers often begin or end a study or survey with the view that it has *now* become so important to map various side-effects of THC and other cannabinoids. Of course this is important since medicine's primary rule is not to inflict harm. But it would be even more satisfying if the insight that young people and other vulnerable people (with a special vulnerability) are also in need of being protected from the harmful effects of cannabis would have had a stronger breakthrough in medicine in general. A third reason could be that politicians and interest groups in many counties have advanced their positions on the legalisation of cannabis, and that this worries researchers with knowledge of cannabis and its known and suspected harmful effects.

It is difficult to evaluate the progress of research in the past five-year period, and we should wait another few years before we do so. The fact that there is a causal relationship between cannabis abuse and schizophrenia/schizophreniform (schizo-

phrenia-like) psychoses has, however, been established when the Swedish studies of national service conscripts were supplemented with a 27-year follow-up during the 2000s and a dozen cohort studies as well as several new surveys on the same subject.

Teenagers – especially the youngest – are a very vulnerable group. This has particularly been shown by the researchers of the New Zealand birth cohort studies. This part of the world in general – Australia and New Zealand – has developed a particularly vital and productive environment for cannabis research in the past 15-year period.

Further progress providing a deeper understanding of the relationship between the dose of cannabis, the plasma level of THC and the level of degradation in cognitive functions has given us a greater understanding of the traffic risks of cannabis smoking. This is knowledge that will gradually be applied within other areas where people handle complicated machinery.

In that researchers on one hand have reported new cases and on the other compiled cases previously reported in the literature, we have obtained an entirely different view of how cannabis causes a risk of inducing acute cardiovascular disease in young people. Both heart attacks (many with fatal outcomes) and strokes/transient ischaemic attacks (TIA) have been reported in young people. An increased incidence of the nearly forgotten condition *cannabis arteritis*, discovered in 1960, has also been reported. It is a periphery inflammatory vascular disease that occasionally exhibits a severe progression.

The treatment of cannabis abuse is not the focus of this report, but it is worth mentioning that the demand for treatment continues to grow. For many years, a workgroup has developed a network for those treating cannabis abusers, with the Stockholm Centre for Dependency Disorders as a base. The number of workgroups is steadily increasing. The network supports the development of working methods, based in part on the manual *Vägen ut ur haschmissbruket* [The Way out of hashish abuse] (T. Lundqvist and D. Eriksson. 1998), as well as general expertise development in the field. In an R&D report, *Ut ur dimman* [Out of the Haze] (Petrell et al 2005), the methodology and some results are described. The same trend of greater demand for treatment has been reported from other countries in Western Europe. Moreover, the number of scientific reports on the evaluation of treatment appears to continue to grow.

Part 1. – General remarks

1. Background and objective

Purpose of this report

This report sums up the state of knowledge regarding the harmful effects of cannabis. "Knowledge" here refers to insights based substantially on research reports, research findings published according to the procedures described in Chapter 3. There is only reason to rely on clinical experience when there is a lack of scientific documentation. Otherwise, I have supplemented the research results with my own clinical experiences in some places to provide illustrations and to lighten up the text.

This report is an update of the Swedish National Institute of Public Health report *Skador av hasch och marijuana: En genomgång av vetenskapliga studier publicerade till och med hösten 2003* [Adverse Health Consequences of Cannabis Use: A survey of scientific studies published up to and including the autumn of 2003]. That report was preceded by the Swedish National Board of Health and Welfare report *Skador av hasch och marijuana* [Adverse Health Consequences of Cannabis Use]. It in turn covered the research literature published up to February 1996. The publication is now being updated and covers research published up to and including 2008.

The topic of this report is limited to the harmful effects of cannabis. In other words, this is *not* a report about cannabis in general, how widespread it is, how it is used, its legal status, its medical use and so on. Nor is it a guide on how to treat or prevent cannabis abuse. The report does not dwell on the very important social interaction between the cannabis abuser and his/her social environment in order to understand the origin of the abuse. Nor is it a position statement in the debate for or against the legalisation of cannabis. However, I do think its contents make a strong contribution to such debate.

At the same time, in the next chapter, I will argue that those who want to understand and act against cannabis abuse in individuals or groups should try to place their knowledge about the harmful effects of cannabis in a wider context. This includes *specifying the problem picture*, as I put it. To facilitate that process somewhat, I will bring up a few aspects of direct relevance to the assessment of the abuse situation. However, this can of course never replace the individual-psychological, family dynamics or social assessments that always need to be done when addressing problems of abuse.

It is my impression that there is a great deal of uncertainty among decision-makers, information officers, youth counsellors, some treatment staff and the general public with regard to the risks associated with cannabis smoking. This is exacer-

bated when a great deal of nonsense intended for young people is disseminated over the Internet while the media bring a considerable amount of objectively unfounded information/propaganda into Sweden from several other European countries in connection with recurring liberalisation discussions.

At the same time, it is young people who are the most exposed to cannabis and other drugs, often in settings where we as adults are in practice barred from entry. Unfortunately, it is also the case – as the reader of this report will realise – that teenagers are in fact more sensitive than other groups to many of the side-effects of cannabis.

Four approaches

Already at this stage, I would like to emphasize four different aspects of the question "how dangerous is cannabis?". This report concerns the first point, but in many cases the other points are also illustrated in connection with the presentation and discussion of research results.

1. The intake of cannabis is associated with a number of risks of harm! Some are acute and tangible. Others have a concealed progression and only present themselves after weeks, months, or perhaps years. Still other harmful effects present after decades. Cannabis has a specific range of harmful effects, which is why it is not usually meaningful to make comparisons with alcohol abuse or tobacco smoking, each of which has its own range of harmful effects.

2. Who is the abuser? An adult or a teenager? If the person is a teenager, is he/she among the youngest teenagers? Does the person seem mentally fragile? Is there a likely vulnerability to mental illness? What are the social circumstances of his or her life? Does he or she have support from parents or siblings, a non-abusing partner or other close adults?

3. What is the pattern of abuse? Are we looking at occasional or highly frequent smoking? Is the abuser dependent? A poly-drug abuser? Does the person appear to identify himself or herself as a drug user?

4. What is the strength (in general) of the preparation? Are we dealing with preparations whose THC concentration (see Chapter 2) is low, or with strong cannabis preparations?

Structure of the report and advice to the reader

The aim has been to account, in a single report, both for conclusions on harmful effects (proven, suspected or excluded) and for the scientific data which support these conclusions. The reader will also receive advice on where to find the original presentations of the research findings to which reference is made (or, in some cases, where to find a previous and generally accepted review).

The major problem has been to produce a text meeting a double requirement: it should be accessible to the interested public, and it should also account for scientific and other facts relating to the effects of cannabis. These facts can be hard to convey without making the text difficult to read and without using an excessive number of technical terms. To facilitate the reading and understanding of the more technical discussions, a glossary has been added at the end.

The first section of the report, *General remarks* (part 1), serves as a kind of introduction. As it has proven difficult to summarise the contents in a brief yet meaningful way, I would recommend the reader to take the time to read the three chapters making up this first part. In the three parts that only deal with the harmful effects of cannabis – *Cannabis and mental disorders (part 2*), *Some psychological and psychosocial harmful effects* (part 3) and *Physical harm* (part 4) – I have inserted **summary boxes** at the beginning of each of the 20 chapters. If the summary given in a box should prove insufficient, a presentation of the relevant research projects – sometimes along with discussion and analysis – can be found in the text. For those who wish to go further, there is of course a list of references, indicating where the various studies can be found. In addition, the table of contents provides an overview of the kinds of harm treated in the report.

After a brief presentation of the cannabis drug and its intoxicating effects, I describe different cannabis preparations and, very briefly, the metabolism of cannabis in the body. In the section called *Specifying the problem picture*, I try to argue for greater awareness of what we are talking about on any given occasion. As has been mentioned above, it is possible to adopt various perspectives within the framework of the overall question. I then provide an account of how scientific findings on the damage to health caused by cannabis are documented. This is followed by accounts of the specific harmful effects provided in parts 2–4 in 19 different sections.

2. Facts on the cannabis drug

"Cannabis" is a generic name for various preparations obtained from the hemp plant, *Cannabis sativa*. *Marijuana* consists of dried plant parts, while the main ingredient in *hashish* is the resin secreted by the glandular hairs found all over the plant, but mainly around the flowers. In addition to these two ancient kinds of preparations, *hashish oil* is produced by means of extraction. Marijuana and hashish are generally smoked. Hashish oil can be used to add strength to the preparations used for smoking, or can be mixed into various foods and beverages. In our part of the world, the absolutely predominant method of taking cannabis is by smoking.

Synthetic preparations of various doses of THC with the occasional addition of other cannabinoids are now available for medical use. These synthetic cannabis preparations are available on the black market in Sweden and are categorised as narcotics under Swedish law.

Of the more than 400 substances contained in cannabis, delta-9-tetrahydrocannabinol (THC) is the most psychoactive substance and is also the main cause of both the euphoric and the negative intoxicative effects as well as several of the harmful effects of the drug. Accordingly, the concentration of THC is not only significant to the intensity of intoxication, but also to the risk of harm. Consequently, discussions of THC concentrations are a recurrent feature of this report.

Strength of the preparations

A little more than two decades ago, the THC concentration of marijuana was generally between 0.1 and 4 per cent, while hashish typically tended to be stronger, at 3–8 per cent. The THC concentration of hashish oil – both in Sweden and abroad – varies greatly, ranging from 20 to 50 per cent. In Sweden, hashish has been the dominant preparation, while the most usual one in the United States and certain other countries has been marijuana. Through manipulation of the growth conditions, varieties of *Cannabis sativa* have been developed with a THC content considerably higher than before. However, it is only since the late 1980s that these stronger varieties seem to have become more widespread. This causes problems both for individuals assessing the risks of use and for researchers trying to compare research findings.

In the opinion of several researchers and clinicians, all the evidence seems to suggest that quite a few of the differences in the occurrence and frequency of harmful effects found by different researchers (especially when comparisons are made between research findings from different countries) can be explained by the fact that the groups studied have been using preparations of differing strength. For instance, the variation between countries in the prevalence of "cannabis-induced psychoses" is deemed to be caused by differing strength of preparations (Newman & Miller, 1992; Meyer, 1975; Ghodse, 1986; Rolfe et al., 1993; Wylie et al., 1995).

Stronger cannabis preparations

A relatively large proportion of existing scientific reports concern studies carried out in the United States in the 1960s and 1970s. The drug abusers studied – like the

participants in scientific experiments – had typically been using marijuana with a THC content of 0.5–3 per cent, whereas marijuana smokers in the late 1980s and in the 1990s have had access to cannabis plants (such as Sinsemilla) with a significantly higher THC content (7-11 per cent according to Schwartz, 1991). These earlier studies may therefore be of a fairly limited value in helping us to understand the harmful effects caused by present-day cannabis abuse in the United States or by both past and present hashish abuse in Northern Europe. In the United States and other countries, it is common in scientific contexts for mention to be made both of the increasing risks and of the influence on research findings. According to official federal statistics, the average THC concentration of cannabis seized in the United States tripled between 1980 and 1997 (Dennis, 2002).

C. H. Ashton reviewed scientific reports and other information from the United States and the United Kingdom. She concluded that all preparations (except hashish oil) were stronger in the 2000s than they were in the 1960s and 1970s:

> Marijuana cigarettes used to contain 1-3 per cent THC (approx. 10 mg per cigarette – "reefer"). Marijuana cigarettes from 2000 contained 6-20 per cent THC (approx. 60-200 mg per cigarette/joint). Hash cookies from 2000 contained 10-20 per cent THC (Ashton, 2001).

At the Swedish National Laboratory of Forensic Science, there is a long-established practice of performing concentration analyses on (random samples of) cannabis which is seized (the results are important for police and customs surveillance purposes). As a result, it is possible, to some extent, to chart changes in the THC concentration levels of preparations available on the Swedish market. When I contacted the laboratory in 1996, I was told that over a ten-year period, considerable changes had been noted in the THC concentration: first, the difference which had previously existed across the board between the stronger hashish and the weaker marijuana had disappeared; second, marijuana was no longer available with the very low concentration levels (< 1 per cent) previously found and its average THC concentration was considerably higher than before, meaning that seizures might be found where the hashish had a THC concentration of 6–8 per cent while the marijuana contained 13–14 per cent THC; and third, both hashish and marijuana now showed a greater spread in their THC concentration – from 1 per cent to 15 per cent (20 per cent) (von Wachenfelt, 1996, oral information). Upon contacting the laboratory this year (2008), they said that both hashish and marijuana shift between a low of 3 per cent and a high of 15 per cent. Marijuana can occasionally have a concentration of 20 per cent.

A marijuana cigarette weighing 0.5 to 1 g thus contains 15–200 mg THC. If it has been treated with hashish oil, the amount of THC may be much greater.

Stronger cannabis in Sweden?

Some countries around the world and in Europe have had an extensive domestic production of cannabis for many years. A few years ago, marijuana production also came to Sweden. Now, it is no longer a question of traditional home cultivation in

a few flowerpots or as a part of a private vegetable patch. In recent years, the police has made a number of seizures of advanced, factory-like indoor crops intended to provide frequent harvests of highly potent marijuana. According to information from a police inspector at the Swedish National Criminal Investigation Department who is well-informed on these matters, Sweden's demand for marijuana is currently satisfied through domestic production.

The fact that a change has occurred is supported by the following:

1. Information from surveillance activities.
2. Seizures of so-called cannabis factories.
3. Seizure statistics. The relationship between the Swedish Customs' and the police's seizures of marijuana used to be stable and constant from year to year. A few years ago, Customs seizures began decreasing while police seizures began increasing.

This change is troubling since higher doses entail an elevated risk of harmful effects. Here, dose size refers to the percentage of THC in the preparation. (In other contexts, we speak of the total dose = lifetime dose, which is also occasionally directly proportional to a risk of harm.)

Some examples of an elevated risk with a high dose:

- The risk of negative effects (feelings of panic, transient psychotic experiences, dysphoria, etc.) of intoxication increases.
- The risk of harm when driving is directly proportional to the size of the dose.
- The risk of toxic psychosis/delirium (profound confusion) increases with high doses.
- The interaction between cannabis and manifest schizophrenia causes more severe consequences at higher doses.

Cannabis intoxication

With a slight generalisation, cannabis can be said to produce two kinds of intoxicating effect. On one hand, there are *positive euphoric effects* with calm, relaxation, a feeling of happiness and a distance to everyday life. On the other, there are *negative alarming effects*, occasionally expressed as panic, dysphoria and mild symptoms of psychosis (hallucinations, paranoia, etc.).

A third type of effects, which can often be objectively demonstrated through testing, is a *degradation of certain mental functions*. These are mainly *cognitive functions* (a degradation of short-term memory, a disruption of cognitive activity, markedly disturbed temporal perception, a distortion of sensory impressions such

as sound, touch and light, a reduced ability to maintain attention, etc.), but also include the disruption of *psychomotor functions*. It should be emphasized that these functional degradations already occur at very moderate and occasional doses.

How cannabis produces its effects on the brain

THC (and some of the other cannabinoids) in the human brain has been found to interact with an entire signal system, the endocannabinoid system. This consists in part of receptors, of which CB1 is the most important in the brain, and in part endocannabinoids, of which the most important is anandamide. The endocannabinoids are substances produced by the body that are chemically related to the exogenous (coming from the outside) cannabinoids, primarily THC. The endocannabinoid system has a number of effects on other signal systems and structures in the brain.

Anandamide binds to the CB1 receptor, activating the electrical or chemical signals associated with the receptor. THC also binds to these receptors, but since THC has other chemical characteristics, a longer binding time and is added in very shifting concentrations, the effects are different. There is extensive ongoing research concerning the endocannabinoid system's internal dynamics and its relationship to various cerebral functions. Moreover, we are obtaining growing knowledge of how THC and other cannabinoids affect the human psyche *through* the endocannabinoid system.

An expression for this interaction is THC's ability to stimulate the individual's emotions in a contradictory manner at different times. Sometimes, THC stimulates euphoria and relaxation, while other times, THC strikes the individual with panic and dysphoria. In other words, there is a strong tendency to a biphasic effect (at lower concentrations, subjectively positive feelings are stimulated, at higher concentrations, anxiety, dysphoria and paranoia). In terms of the calming effects of cannabis, there is also an interaction of another cannabinoid, cannabidiol (CBD), which exists in low concentrations in various subspecies of the cannabis plant. CBD has an antagonistic effect on THC (Ashton et al 2005, Fabrício et al 2008).

The Metabolism of THC – Duration of Intoxication

When cannabis is smoked, the THC level in the blood rises quickly, reaching its maximum within a few minutes. If the drug is taken by mouth and stomach (e.g. by eating cookies or chocolate containing cannabis), the maximum THC level is achieved after 30 to 60 minutes (depending on whether the taker is fasting or not). The bio-availability is approximately 50 per cent when smoking (regular smoker) and one third as large as the intake from eating the preparation. The maximum subjective effect more or less coincides with the blood level, even though a minor delay has been observed. The duration of intoxication after a single dose is directly dependent on the size of the dose and manner of intake. If the dose is low, the effect lasts for a few hours if the drug is inhaled and just over twice as long if it is eaten. The blood level of THC falls rather quickly, partly because of conversion into metabolites and partly because of distribution to fatty tissue (Grotenhermen,

2003). The half-life for THC in plasma is approximately 56 hours for the one-time user, while those with chronic abuse/dependence have a half-life that is half as long. The half-life of THC in tissues (mainly fatty tissue) is approximately seven days. The total elimination period from fatty tissue can also be up to one month after a single intake (Ashton 1999). With repeated intake, high concentrations can gather in the fatty tissue and from there affect the brain (Pope et al 2002). How long is not known.

Relatively little is known about this phase of the metabolism; for instance, it is unknown how much THC and metabolites are stored in fatty tissue. The THC later secreted back into the blood stream *probably* does not reach any high concentrations. However, we know that the brain can be affected for some time after the level of THC in the blood is no longer measurable. This effect probably lasts longer with higher doses and the longer an intensive period of smoking has lasted. Considering that our knowledge is so limited – especially in connection with continuous cannabis intake – one should be cautious and apply broad margins when estimating how long and how much the individual is affected. In addition, the metabolism of cannabinoids is highly affected by individual, unknown factors.

THC breaks down into a large number of metabolites. In terms of volume, the predominant one is THCCOOH, which is non-psychoactive. One of the intermediate steps in its formation is 11-OH-THC. Both THC and 11-OH-THC are short-lived but psychoactive, whereas the largest metabolite, the non-psychoactive THC-COOH, remains in the blood considerably longer. Accordingly, many of THC's metabolites are stored in fatty tissue and then slowly re-secreted. The breakdown of THC into metabolites in the liver and kidneys makes it possible to measure these metabolites in urine for up to weeks after intake. The longest length of time registered was 77 days, which occurred after very prolonged intake of high doses of cannabis.

One of the core problems with regard to the acute effects is that some of us have activities that appear to be very sensitive to even moderate reductions in cognitive ability. In terms of the ability to operate a motor vehicle, systematic studies have been done where various levels of THC in the blood (expressed in nanograms/ml) have been related to tests of cognitive and psychomotor functions that are relevant to the ability to handle a motor vehicle. These experiments generally investigated the effect of a single moderate dose. In terms of the effects of chronic smoking, we know significantly less (Harrison G.P. et al 2002). Another activity investigated in a few studies is the (aircraft) pilot profession, which requires the ability to remember and combine a number of different signals into a whole and to properly carry out a series of manoeuvres in the correct order. As will be seen in Chapter 16, pilots showed impaired ability 24 hours after taking a moderate dose of cannabis, and several hours after THC in the blood dropped below measurable amounts (Leirer, 1991). For example, making a landing with a modern aircraft requires a great deal of the pilot's cognitive skills. Leirer (1991) reminds us that *driving under difficult conditions* presumably entails the same high demands.

Otherwise, few studies have looked at the relationship between the influence of cannabis and other professions. Ashton (2001) points out that, for example, professionals such as anaesthetist doctors and nurses have to some extent similar tasks: to carry out, during a short period of time, a series of actions, in the correct order and precisely "dosed". Indeed, our high-speed and high-tech society is based on a large number of people having roles involving similar requirements.

Cannabis smoking – a potent symbol

In the 1960s and 1970s, when cannabis became a widely spread drug in the industrialised societies of the Western World, the use of cannabis became a potent symbol for large groups of young people. Here, I will not discuss the links between cannabis and flower power, the hippie movement, different music styles and youth revolt in general.

It is, however, obvious that some of this symbolic potency and the romantisation of this substance remains even today, and that an awareness of the main features of the origins of cannabis abuse as a societal phenomenon is important if we are to be able to understand the situation facing us today. One of the very best books available describing the history of interaction between individuals' needs on the one hand and cultural and economic conditions on the other is *Hasch: Romantik och fakta* ["Hashish: Romanticism and Facts"] by Thomas Nordegren and Kerstin Tunving (1984).

Specifying the problem picture

It is a far too common occurrence that cannabis and its risks are discussed in general terms without any form of specification. What are the circumstances? Who is the abuser? What does the pattern of abuse look like?

THC Content

As was mentioned in the section on the different preparations, the THC content of cannabis varies considerably, depending on the kind of preparation, among other factors. Differences are also found between different sorts of the same kind of preparation, especially between different types of marijuana. Many of the harmful effects are dose-dependent – which is not to say that this is the only factor that determines the intensity of a side-effect..

Sporadic or chronic abuse

The acute effects of cannabis intoxication, especially in high doses of THC, have a very clear impact on the taker's experiences and functional ability in different respects. Certain subjective intoxication experiences, which are characteristic of isolated occasions of intoxication, disappear or change when the abuse becomes chronic in nature. However, the same *functional impairments* remain, and new functional impairments make their appearance as manifestations of chronic effects.

Whether or not the taker is dependent (see Chapter 5) seems to be very important in determining how difficult it is to stop abusing. The risk of many harmful effects increases further if dependence is present.

Differential risk of harm from cannabis

The risk that cannabis abuse will cause harm varies from individual to individual, because people's vulnerability varies. This interaction between stress or trauma on the one hand and vulnerability on the other is valid for many diseases and kinds of harm. The problem is that individual vulnerability to any given type of stress or trauma is usually unknown. That being said, as far as the effects produced by cannabis on humans are concerned, we do know that certain groups are significantly more likely than others to be harmed. This applies mainly to the following three groups:

1) Teenagers

Anything in excess of occasional cannabis smoking presents a threat to the development of young people, owing to the way in which THC interacts with the inner psychological processes that characterise the teenage years. Several factors, not least the inner mental imbalance which is a feature of that developmental period, make teenagers more likely than adults to react with psychiatric symptoms. Also due to the fact that the body is still developing during the teenage years, young people run a greater risk of mental and – we believe – physical harm. A great deal indicates that the inclination to harm is greater the earlier use begins. Teenagers also often have less adult support because of the emancipation process from their parents' generation (also see Chapter 15).

2) Pregnant women/unborn children

Since THC passes from the mother's blood into that of the foetus, the latter is exposed to an increased risk of harm if the mother smokes cannabis while pregnant. If the mother also uses or abuses other substances such as tobacco or alcohol, a summation effect can be expected.

3) People with a disposition towards mental disorders

Cannabis smoking can provoke, cause relapses into and worsen a number of mental illnesses and disorders. This is clearly illustrated in the chapters on psychosis and depression. For example, cannabis smoking entails a large risk of deterioration and relapse in people with a schizophrenic condition. Vulnerable individuals have an elevated risk of the onset of psychoses with cannabis smoking.

Medical uses of cannabis

Intensive research is being carried out to test the hypothesis that the cannabinoids (and other substances contained in cannabis) have curative effects. Even though there is no direct link between this research and that on the harmful effects of can-

nabis, the two fields are sometimes confused in the public debate, which I think is unfortunate. In fact, what we are dealing with here are two entirely separate medical fields which could, at best, cross-fertilise each other.

The opiates (including morphine) have long been, and still are, our most effective analgesics, and they have formed the basis of a series of synthetic preparations with a strong analgesic effect. This use of morphine and preparations derived from morphine to relieve pain, however, very rarely gives rise to drug-policy discussions where the abuse of morphine or heroin and the medical prescription of opiates are grouped together as a common evil. Nor do we hear the argument that, because opiates are used for medical purposes, we do not need to worry about the illegal use of opiates.

3. How to find information about the harmful effects of cannabis

How can one obtain somewhat comprehensive knowledge on the harmful effects of cannabis? Is there any guarantee that any important research findings have not been overlooked? What is the proper course of action if there are no research results in a certain field? And what should you do if different teams of researchers have obtained different results?

"Knowledge" here refers to insights based substantially on research reports, research findings published according to the procedures described below. There is only reason to rely on "clinical experience" when there is a lack of scientific documentation. Otherwise, I have supplemented the research results with my own clinical experiences in some places to provide illustrations and to lighten up the text.

Scientific documentation in international reports

By going through previously published summaries of the state of research and by searching for information in scientific databases, I have been able to obtain a satisfactory coverage of research reports published up to and including the autumn of 2008.

Since many of the side-effects of cannabis are directly or indirectly medical, my approach has been to carry out literature searches of the medical database MEDLINE, including the additional resources contained in PubMed. (MEDLINE is the US National Library of Medicine in computerised form.) I have also used the Swedish database Alcona administered by the Swedish Council for Information on Alcohol and Other Drugs (CAN).

Although the practice of storing articles from scientific journals in electronic databases has considerably facilitated the task of searching the literature, it would hardly be possible to find one's bearings among the thousands of scientific works produced without also having access to a number of reviews compiled in previous years. These reviews have generally been produced by teams of experts working on behalf of national or international healthcare organisations. Some of the most important such reviews (in order of the year of publication) are:

Chronic Cannabis Use (Dornbusch R. L. et al Eds. 1976)

Marijuana: Research Findings (Petersen R. C., NIDA, 1980)

Report of an ARF/WHO scientific meeting on adverse health and behavioral consequenses of cannabis use (1981). This is a summary of cannabis and health hazards.

Marijuana and health (Institute of Medicine, 1982)

Cannabis and health hazards. Proceedings of an ARF/WHO scientific meeting on diverse health and behavioral consequences of cannabis use (1983)

Cannabis och medicinska skador: en nordisk värdering [Cannabis and adverse medical effects on health: an evaluation from the Nordic countries] (1984)

The health and psychological consequences of cannabis use (Hall W. Solowij N. Lemon J. 1994)

Cannabis: a health perspective and research agenda (WHO, 1997)

The Health Effect of Cannabis (Kalant H. et al Eds. 1999)

A cannabis reader: global issues and local experiences (EMCDDA, 2008)

Of course, there is also a large number of textbooks that also summarise the scientifically established harmful effects. Mention will be made here of two such books:

Cannabis use and dependence: public health and public policy (Hall W. Pacula R. 2003)

Marijuana and madness, psychiatry and neurobiology (D. Castle, R. Murray. Eds. 2004)

Literature search in concrete terms

Since this is the third edition of this survey, the literature searches have been conducted in many ways. At an early phase, since I only had a background based on clinical experience and small searches prior to a few previously published textbooks in the drug addiction treatment field, the aforementioned surveys in report form meant more as an initial orientation in a certain field.

It is usually necessary to read the original articles in order to weigh up and analyse the research findings for oneself. A common approach to obtaining an all-round understanding of a scientific issue is to start with a review that is as recent and authoritative as possible, and then work one's way backwards in the traditional manner, using the review's list of references as a guide.

More recently, it has taken less time to go directly to library searches. In the course of the work, I have learned more and more about the research field and which researchers and research groups have been leading in their respective fields, and consequently, it has occasionally been appropriate to search by a researcher's name.

Since most of the side-effects of cannabis are directly or indirectly medical, my approach has been to carry out literature searches of the medical database MEDLINE, including the additional resources contained in PubMed. (MEDLINE is the US National Library of Medicine in computerised form.) For books and some reports, I have used the Alcona database at CAN's library. I have also visited LIBRIS on occasion. I have also received help from the Swedish National Institute of Public Health and thereby been able to conduct a few searches on PsykINFO.

Consequently, there have been many paths to the main source of PubMed: searches for a certain work, for a certain author's publications or, mainly, for a topic/type of harm.

My searches have most often been unsophisticated and brief. The most common type of search, with the intention of bringing my knowledge up to date within a certain sphere could look like this, for instance: (cannabis OR marijuana OR hashish) AND (depression OR "depressive disorder" OR "major depression"). In an initial round with a limitation to reviews and with a limitation in time that agrees with my previous search (e.g. articles a maximum of two years back in time) in the field.

Research reports and quality assurance

Is there any assurance that an article published in a prestigious journal is of acceptable quality? To begin with, before a research department allows an article to be sent off for publication, it is generally subjected to an internal process of review and criticism. Moreover, scientific journals also review articles submitted – not seldom in a heavy-handed way – with regard to their method and their analysis. Most researchers have had articles returned to them accompanied by a letter from an editor suggesting a more or less extensive reworking of the article or turning it down flatly because of insufficient quality. At the same time, however, we have to realise that there is no such thing as an absolutely perfect study that cannot be questioned in any respect.

Scientific works that have been published, however, must be assessed and compared from the perspective of the quality of the design which has been used and how well supported the conclusions are. Two studies relating to the same question may have entirely different weight as evidence. Sometimes, help in this evaluation is provided by the study in question being a part of a review. A researcher or research group well informed in the issues has then made a comparison and evaluation of a number of studies on the same issue.

In the section on schizophrenia, I have related some central remarks on what characterises a good cohort study according to M. Susser (1991) in the aim of evaluating a causal relationship. This was done because the cohort study is one of the most common types of studies to establish a causal relationship in the problem area treated in this knowledge survey.

Part 2. Cannabis and mental disorders

4. Damage to mental health – an overview

Summary of Chapter 4

Cannabis is one of the most psychopathogenic of all narcotic preparations. Co-morbidity and interaction with mental illness/disorders are common.

The following mental disorders/illnesses are relevant here in that it is considered that they can be caused, precipitated from a latent state or exacerbated by cannabis abuse:

- Development of dependence
- Psychoses:
  - Toxic psychoses
    - Cannabis-induced psychosis
    - Cannabis-induced delirium
  - Functional psychoses
    - Schizophrenia
  - Schizophrenia-like psychoses
- Affective disorders:
  - Depression
  - Manic conditions
  - Suicidal behaviour
- Anxiety disorders
- Depersonalisation syndrome
- Amotivational syndrome
- Impulsively violent behaviour

Like other sedative drugs of abuse, cannabis has the "ordinary" effects of relaxation, calming, a feeling of happiness and distance from everyday concerns. In addition to this, it also produces more dramatic effects on the psyche: fragmentation of thought processes, severe disruption of temporal perception, a feeling of being able to be in several places at the same time, a marked sense of separation from other people and from ordinary life (a "glass-wall feeling"), and where very high doses are involved

also, if not always, mild and temporary psychotic symptoms – hallucinations and delusions. Given these very special – mind-fragmenting – effects, it is not surprising that associations are found between cannabis and various mental illnesses.

Cannabis is in fact one of the most psychopathogenic narcotic preparations that give rise to mental illness to the greatest extent. Owing to the widespread use of cannabis, this fact has serious consequences for both individuals and society. Consequently, extensive research is being done on dual disorders with cannabis abuse.

Dual disorders and other interactions with mental disorders

In the past two decades, the phenomenon of dual disorders has received growing attention in psychiatry and abuse treatment. Substance abuse and one or more mental disorders appear at the same time.

Such dual disorders are common with cannabis abuse. A few years ago, the results were published from a large interview study of dual disorders directed at 43,000 representatively chosen adult Americans (Stinson F.S. et al 2006). In the group of cannabis users with abuse or dependence in the past year, a high degree of dual disorders in the three largest disease groups was found:

Affective disorders
(various types of depression and manodepressive disorders): 30 per cent

Anxiety disorders
(panic anxiety, phobias, obsessive-compulsive syndrome, etc.): 24 per cent

Personality disorders
(antisocial, schizoid etc. personality disorders): 48 per cent

Psychotic illnesses were not included in this study. However, we know that more cannabis abusers can be found with concurrent psychotic illnesses than among non-abusers. In her dissertation *Psykotiska patienter med missbrugsproblemer* [Psychotic patients with problems of substance abuse], Birgit Jessen-Petersen presents a cross-sectional study that comprised approximately half of Copenhagen's outpatient and inpatient medical and social institutions where psychotic patients and clients with substance abuse problems are treated. Of the 321 schizophrenic patients/clients in treatment, 6 per cent were cannabis abusers. Of the 50 with another psychosis diagnosis, 12 per cent were cannabis abusers. Of the patients with an affective disorder, less than 1 per cent abused cannabis.

When she conducted a simultaneous study of psychotic patients with and without cannabis that sought emergency psychiatric care during a period of three months, she found the following: among those with schizophrenia, 19 per cent also had cannabis abuse; among those with affective psychoses, 2 per cent had cannabis abuse; among those with "other psychoses", 24 per cent had cannabis abuse and among

the non-psychotic (which had extensive substance abuse, primarily alcohol), 2 per cent abused cannabis (Jessen-Petersen B. 1994).

The harmful effects of drug abuse with dual disorders can be roughly divided into two categories: *non-specific effects*and *specific effects*.

General *non-specific effects*, refer to effects such as a diminished ability to contribute to treatment, take care of one's social situation, take care of one's physical health, etc. This kind of effect can be found in every type of alcohol or drug abuse. *Specific effects* refer to effects where cannabis exacerbates the mental illness through neurophysiological effects.

The studies that have tried to answer the question as to whether or not cannabis has *caused* or *induced* the mental disorder focus on an extremely important aspect of generally neurophysiological specific effects.

Different types of relationships between cannabis smoking and mental illness

L. Degenhardt, among others, believes that three different types of relationships can be distinguished between cannabis abuse and mental illness in the progression up to dual disorders (Degenhardt L. et al 2003).

1. Cannabis exerts its own independent influence that induces/causes the mental illness, or clearly contributes to the origin of the disease.
2. A condition of mental illness encourages the individual to begin smoking cannabis. One hypothesis is that, in such cases, it is a type of *self-medication*, against symptoms of illness, against the side-effects of medication or against dysphoria induced by the disorder. Another alternative is the fact that it seems as if psychotic patients have taken up cannabis smoking as a way of gaining access to a social community. Some may also presumably begin smoking cannabis for the same reasons as healthy young people.
3. The same background factors cause both the mental illness and the cannabis abuse, a biological (e.g. genetic) factor or a psychosocial familiar factor. Here, there are also certain mental disorders/illnesses that have a strong tendency to generate both drug abuse and other mental disorders. Examples of this are attention-deficit hyperactive disorder (ADHD) or antisocial personality disorder.

It is obviously crucial, for a variety of reasons, to have as comprehensive knowledge as possible about the association between cannabis abuse and mental disorders. It is particularly important to be aware of a possible causal relationship between cannabis smoking and a certain mental disorder as well as how large the risk is of triggering the disease. This is important for all measures taken in a public-health perspective, ranging from drug-policy decisions to the design of treatment interventions aimed at individual abusers. Regardless of what the cause is and what the effect is, the two conditions generally tend to have a negative influence on each

other. In addition, the combination of drug abuse (including cannabis) and mental illness is an extensive problem in psychiatry and substance abuse treatment. It is also well known that these patients with dual disorders generally have worse prognoses than those only burdened by one problem.

Classification of mental disorders/illnesses known or suspected of interacting with cannabis smoking

The following mental disorders are known or suspected to be associated with cannabis abuse in that the abuse may cause the mental disorder, precipitate a latent mental illness or exacerbate an existing illness/disorder. The development of *dependence* naturally plays a special role, but is included in the list because it is formally an illness:

- Dependence
- Psychoses:
  - Toxic psychoses:
    - Cannabis-induced psychoses
    - Cannabis-induced delirium (acute confusional state)
  - Functional psychoses:
    - Schizophrenia
    - Schizophreniform psychosis
- Affective disorders
  - Depression
  - Manic conditions
  - Suicidal behaviour
- Anxiety conditions
- Depersonalisation syndrome
- Amotivational syndrome
- Impulsively violent behaviour.

The following chapters may present some difficulty to readers who are not familiar with psychiatric terminology. However, I have not judged it possible to include an introduction to psychiatry in this report. I regret this and express my hope that the glossary added at the end of the report may be of some help.

5. Development of dependence in cannabis abusers

Summary of Chapter 5

Cannabis abuse can evolve into cannabis dependence, which is characterised by three of the following seven criteria:

1. Tolerance (the abuser needs successively greater amounts to achieve the same effect).
2. If intake is discontinued, withdrawal symptoms arise.
3. Cannabis is often used in larger amounts or for a longer period of time than intended.
4. There is a lasting desire to or repeated attempts to end the cannabis dependence.
5. A great deal of time is spent trying to get a hold of cannabis, use it and recover from intoxication.
6. Important social, professional or leisure activities are abandoned or cut back.
7. Use continues even though social, physical or mental problems worsen.

Accordingly, dependence is associated with a withdrawal syndrome that expresses itself upon attempts to quit. These symptoms arise after 1-2 days, peak after 2-4 days and subside in 2-3 weeks.

Common symptoms include restlessness, anger, irritability, loss of appetite/weight, nervousness/anxiety and difficulties sleeping.

The proportion of cannabis abusers who become dependent has been found to vary considerably in different studies, but is surprisingly high on average. Of those who smoke cannabis at least once, 10 per cent will develop dependence at some point in their lives.

Cannabis-dependent people have difficulties in quitting, are more at risk of being affected by the harmful effects of cannabis smoking, and are also more likely to move on to other illegal drugs.

The level of risk of cannabis use is highly dependent on how intensive use is. The intensity reflects how free or unfree the person is in relation to the drug.

In clinical practice and research contexts, the terms of use, abuse and dependence are used in accordance with international criteria described in the diagnostic manuals, *International Classification of Diseases* (ICD-10) and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM IV). (As known, we use these terms in another manner in daily use. "Abuse" may, for example, describe all three levels.)

Use: Sometimes in daily speech, we try to emphasize the difference between this level and the other two, which describe actual disorders, by adding terms. Examples of this are "occasional use", "recreational use" and the like. These terms are often adequate, but sometimes perform a euphemistic function.

Abuse: Abuse involves individuals causing physical, mental or social harm – to themselves or to others – through their use of the drug. At the abuse stage, use of the drug is not constant; the individuals have a degree of control over their drug use and are periodically able to abstain from using the drug.

Dependence: At the dependence stage, the abuse has evolved into a compulsive need for frequent or constant intoxication. The dependent person ignores harmful social, mental or physical effects, and spends considerable time to obtain the drug, take it and deal with the after-effects. Other interests are increasingly relegated to second place, and attempts to break the dependence often fail. Dependence can give rise to a *withdrawal (abstinence) syndrome* with withdrawal symptoms when the dependent person tries to quit.

Despite clinical observations of signs of both dependence and withdrawal symptoms, it took rather long to prove conclusively that cannabis smokers develop not only abuse but also dependence.

A relatively large number of experiments were carried out in an attempt to prove the occurrence of tolerance and withdrawal symptoms (cannabis was given to subjects for a certain period of time, and then the effects of interrupting the supply were studied). Initially, these attempts failed. In many cases, for ethical and other reasons, the doses given were unrealistically low and the periods of study were short (Hollister, 1986). When Jones and Benowitz (Jones, 1983) gave significantly higher and more frequently administered doses during a three-week period, their subjects rapidly developed tolerance and manifested a withdrawal syndrome very similar to that observable in clinical work.

Since then, a large number of systematic observations and studies have been made that support the clinical picture and the experiments: dependence develops in association with long-term and frequent use (Miller & Gold, 1989; Gable, 1993, Comton et al 1990). The withdrawal syndrome was also registered. An extended period of frequent cannabis use results in withdrawal symptoms when abuse is discontinued. Commonly occurring symptoms include sleeplessness, anxiety, irritability and occasionally perspiration, slight nausea, trembling and weight loss (Comton et al., 1990). The sleeplessness experienced can be particularly troublesome and often causes relapse in people who try to give up cannabis. The intensity of the discomfort experienced depends on the size of the dose and the frequency and duration of abuse (Comton, et al., 1990, Duffy & Milin, 1996; Crowley, et al., 1998; Haney, et al., 1999).

In addition, some reports have been published which describe more serious withdrawal symptoms, especially psychotic symptoms of a manic-depressive nature (Teitel, 1971; Rohr et al., 1989).

The nature of cannabis dependence: withdrawal symptoms, the progression of the withdrawal syndrome over time, etc.

However, a sense of doubt has remained in some circles. *The question of what the nature of dependence is in cannabis abuse is important to the understanding of the strength and mechanism in dependence as well as to how dependent persons should be supported to successfully become drug-free.* Consequently, I will delve a bit deeper mainly into A.J. Budney's and his colleagues' research results. Over a 15 year period, this group conducted a series of studies that illustrate various aspects of cannabis dependence. Their research also touched on the treatment of dependence, which is outside the scope of this survey, however.

About the withdrawal syndrome:

- Begins within 24 – 48 hours with the maximum intensity on the second to fourth day. Subsides within three weeks (Budney et al. 2003).
- The syndrome ends if a sufficiently high dose of THC is administered orally. Tested and matched against a placebo (Budney et al. 2007a).
- Withdrawal symptoms – as per the list below – have been registered a) in experimental situations (e.g. like those above), b) in the home environment of abusers, c) through systematic interviews with groups of dependent abusers conducted at outpatient clinics and d) in interviews with relatives (Budney et al. 1999, Budney A.J. 2006, Vandrey et al 2005).

Withdrawal symptoms:

Commonly occurring:

- anger, aggressiveness
- loss of appetite and weight loss
- irritability
- nervousness/anxiety
- restlessness
- difficulty sleeping including “strange dreams”.

Less common symptoms:

- chills
- dejection
- stomach pains
- shakes
- sweats.

In summary, cannabis gives rise to dependence and a withdrawal syndrome that comprises emotional and behavioural disturbances. It is a matter of a significant withdrawal syndrome, although less pronounced than with heroine, alcohol and cocaine dependence (Budney A.J. 2006).

How widespread is cannabis dependence?

Answers to these types of questions regarding frequency (prevalence) have been sought in the scope of the large North American population study, the Epidemiologic Catchment Area (ECA) Study. Of the 20,000 respondents, 4.4 per cent showed signs of abuse or dependence (*cannabis use disorders*). According to generally accepted criteria, 2.7 per cent were dependent (Hall, et al., 1994, p. 116).

In the latter study from the United States, Compton et al (2004) presented a large study in the scope of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). The group studied comprised 43,000 people who were representative of American men and women over the age of 18 and pertained to the years 2001-2002. Results: 4 per cent had smoked cannabis in the past year. Only 0.4 per cent met the criteria for dependence in the past year. The relationship between abuse and dependence was 3 to 1 with the higher figure for abuse. If the whole issue is turned around and the question posed is how large a proportion of those who used cannabis also were dependent in the past year, the figure is 35.6 per cent.

The NESARC study also had a general objective, to be able to form the basis of a comparison with a study conducted ten years earlier and comprised roughly as many Americans over the age of 18 (Comton et al 2004). Cannabis use was found to be largely unchanged (a 0.1 per cent increase) while the figures for abuse and dependence had increased by 0.2 and 0.1 per cent, respectively.

A remarkable change during the ten-year period was the higher proportion of the users that were abusers or dependent. This was an average increase of 5 per cent. This increase primarily exhibited itself among the youngest users. This change over the ten-year period is seen as an expression of greater user among the youngest. According to Comton, several researchers have shown that this means a faster transition to abuse and dependence. According to the researchers, another cause may be the 66 per cent increase in the THC strength during the period, which also results in a faster dependence.

In 2001, W. Swift et al reported on a similar national Australian study. Slightly more than 10,000 people over the age of 18, representative of the population, were studied. In the past year, 1.5 per cent had been dependent and 0.7 per cent were abusers. Of the 7.1 per cent that were cannabis users at some level, approximately 20 per cent were dependent and roughly 10 per cent were abusers.

In the cannabis monograph published by the Australian National Drug and Alcohol Research Centre (Hall et al., 1994), there is an extensive and very thoroughly drafted section on cannabis dependence. The authors first emphasize that various groups (differentiated by gender, age, social status and so on) are at different levels of risk of developing dependence. They then establish that the literature

review lends support to the rule of thumb that anyone who has begun smoking cannabis has roughly a 10 per cent risk of developing dependence during some period of their life.

Consequences

Whether a particular drug can or cannot give rise to dependence is a very important issue. The risk of harm increases considerably for an individual who is no longer able to control his or her drug use. First, it becomes more difficult to quit the abuse, as stated above. As has previously been pointed out, most of the harmful effects dealt with in this report are dependent on the frequency and duration of abuse. Therefore, those dependent on cannabis run particularly high risks. The tangible effects arising from long-term abuse are the kinds of cognitive damage discussed in Chapter 14. As pointed out in Chapter 15, dependence in teenagers puts important aspects of their development towards adulthood at risk. An abuser who has become dependent will often ignore social damage (such as damage relating to work, education and family relationships). Moreover, a cannabis-dependent person can be expected to act in a riskier manner towards others, for example, by driving a car under the influence. Hendin (see Chapter 14) also stresses a number of risk factors which are exacerbated by long-term use.

Some researchers, including Kandel and Davies (1992) and Fergusson et al. (2000; 2002), have also shown that the link to other kinds of abuse – of both other illegal drugs and alcohol – becomes much stronger as a person progresses from sporadic to very frequent cannabis abuse.

A further aspect which it is important not to disregard is the "mental corruption" caused by the life situation of the dependent persons: for years on end, as well as having to hide their abuse from outsiders, they must come up with explanations and excuses for themselves and their family in order to be able to continue their abuse.

6. Cannabis and psychoses – an overview

Summary of Chapter 6

Cannabis has occasionally been counted among the hallucinogenic preparations. Hallucinations and paranoia sometimes appear during normal intoxication, especially at high doses. Therefore, it is reasonable to expect side-effects in the sphere of psychotic disorders.

This chapter discusses the following relationships between cannabis smoking and psychotic and near-psychotic conditions:

Cannabis-induced (toxic) psychoses or similar conditions:

- cannabis-induced psychosis
- cannabis-induced delirium (acute confusional state)
- is there a connection – over time – between short-term cannabis-induced psychoses and schizophrenia?

Functional psychoses:

- cannabis and schizophreniform psychosis
- cannabis and schizophrenia

Other:

- How does cannabis affect already established schizophrenia? "Self-medication"

Short-term psychotic disorders – cannabis-induced psychosis and cannabis-induced delirium – are considered to be toxically triggered and the conditions have a good prognosis if cannabis abuse ends. Knowledge about these cannabis-induced manifestations is based on case studies and generally not on long-term controlled studies.

A Danish study has given us reason to question the strict delimitation made for many years between the short-term cannabis-induced psychoses and the schizophrenic/schizophreniform psychoses. It is possible that there is a causal relationship between these conditions over time.

Cannabis and schizophrenia

After the Swedish "conscription study" was published in 1987, in its footsteps in the 2000s, a large number of well-designed observation studies (cohort studies) from several countries showed that high consumers of cannabis have an elevated risk of schizophrenia or *schizophreniform psychosis*. The increase in risk – which is greater among vulnerable individuals – is larger the higher the combined dose the individual has consumed is.

The co-morbidity of cannabis with psychotic conditions is doubtless one of the most alarming aspects of what is gathered under the heading "harmful effects of cannabis". In the following four chapters, I will account for how the scientific community views this relationship today. Occasionally, I will also refer to my own clinical experience. This includes illustrations with some descriptions of a case of my own.

Two types of psychoses: toxic psychoses and functional psychoses

The toxic psychoses are divided into *cannabis-induced psychosis* (occasionally called hashish psychosis or cannabis psychosis) and *cannabis-induced delirium* (occasionally called acute confusional state). Cannabis-induced psychosis always has more or less of an element of delirium (profound confusion), but psychotic symptoms such as hallucinations and delusions are dominant, although not cognitive disruptions. *Cannabis-induced delirium* is dominated by confusion and disorientation with elements of psychosis. The two conditions always have an onset in association with cannabis intake. (Castle and Ames (1996) consider these conditions to be expressions of encephalopathies – temporary brain damage.) Progression is short lived if the abuse is discontinued.

The others are the so-called functional psychoses. The term "functional" refers to the absence of any known organic damage. Today, we would have to say that there probably are organic components, but more in the form of a subtle neurophysiological disturbance whose nature we know rather little about, but which has resulted in a greater vulnerability for psychotic disorders. In the toxic group, the direct effects on the brain are notable in elements of muddled consciousness (delirium), with distinct confusion, memory disruptions, etc. These symptoms are absent from the functional conditions. Instead, cognitive effects occur together with other psychotic symptoms. They arise a short time, or longer time – up to several years – after the beginning of cannabis use. Smoking has often been intensive. These psychoses often have a chronic or, in any case, extended progression. An appropriate division is schizophrenia and schizophreniform psychosis. However, growing numbers of researchers believe that it is commonly a question of a type of long-term, fully or partially cannabis-induced functional psychosis – schizophrenia.

Now, let us pause and point out that, based on a Danish study (Arendt et al 2005), the strict division into short-term toxic psychoses on one hand and the functional schizophreniform psychoses and, generally long-term, schizophrenia on the other has been in question for some time. In a more long-term perspective, there may be a causal relationship between most of the short-term psychoses and schizophrenia/schizophreniform psychosis. This issue is discussed in Chapter 8, "Cannabis-induced psychoses".

It should be underlined that what we are dealing with here are the most profound disturbances known to psychiatry; even when they are short-lived, such disturbances can leave marks on those affected and on their families which may remain for many years or even be of life-long duration. By definition, these conditions are of a combinatory nature: there is both an abuse condition and a serious mental dis-

order (see dual disorders in Chapter 4). These "dual disorders" are among the most difficult to assess in the whole of psychiatry. Moreover, conditions of this type often make demands on the most costly resources.

The following relationships between cannabis and psychotic/near-psychotic conditions are discussed here:

Toxic psychoses:

- Cannabis-induced psychosis
- Cannabis-induced delirium (acute confusional state)
- Is there a connection over time between short-term cannabis-induced psychoses and schizophrenia?

Functional psychoses:

- Cannabis and schizophreniform psychosis
- Cannabis smoking as a cause of schizophrenia

Other:

- How does cannabis affect already established schizophrenia? "Self-medication"?

Older scientific and clinical reports of a surveying nature

The following studies constitute support for the existence of some type of connection between cannabis and psychoses and psychotic symptoms, together with studies (often of a later date) that are presented in the following chapters. Altogether, these early studies can be described as surveying and hypothesis-generating. These case studies, clinical observations, cross-sectional studies, local prevalence studies, etc. say nothing about a *causal relationship* in either direction between cannabis and schizophreniform psychoses. Such studies are presented in the later chapters.

In her dissertation entitled The Prognosis of Drug Abuse in a Sixteen-Year-Old Population, Maj-Britt Holmberg found that of those young people who had been consuming large quantities of drugs (almost exclusively cannabis) at the age of 16, 10 per cent had a case record as psychosis patients eleven years later. This proportion is of course many times larger than that which would be expected in a normal group of young adults (Holmberg, 1981). In another study, a group of 908 patients were examined from a number of different viewpoints in connection with their admission to two psychiatric hospitals in London. Of the 496 patients who agreed to undergo an examination including a urine test for cannabis, it was found that among those testing negative for cannabis, 62 per cent were diagnosed as having psychosis, whereas 88 per cent of those testing positive for cannabis received such a diagnosis (Mathers et al., 1991).

Bier and Haastrup (1985) found, in their study of all patients admitted during one year to a psychiatric unit at one of Copenhagen's hospitals, that 30 patients had cannabis-provoked psychoses, i.e. psychoses where it was deemed that cannabis smoking had contributed to precipitating (or causing a relapse into) psychosis. The authors conclude that in a population of 100,000, it can be expected that 15 patients per year will be admitted to hospital with psychoses precipitated or caused by cannabis. The group of patients included both people with no other mental disorder (toxic cannabis psychoses), schizophrenics and people with personality disorders. In the late 1960s and early 1970s, Tennant and Groesbeck (1972) studied American soldiers stationed in Europe. In 1969 a major wave of drug abuse, dominated by strong cannabis preparations (hashish), started among these soldiers. During the years 1969–1971, the authors found that, in addition to a series of other acute negative reactions, the number of people afflicted by *schizophrenic reactions* (acute psychotic reactions which did not necessarily have to lead to what we mean by schizophrenia) increased from 16 in 1968 to 77 in 1971 – i.e. an almost five-fold increase in four years. The researchers' impression was that the smoking of hashish was the most important contributing factor in these psychotic reactions.

Otherwise, the majority of studies presented in the following sections on psychosis also provide support for the existence of a link between cannabis and psychoses.

A North American study of cannabis-smoking young people in the first half of the 1970s (Weller & Halikas, 1985) can be mentioned as an older representative of the minority of studies where no association was found between cannabis smoking and psychosis (or other serious mental disorders). However, owing to the low THC concentrations prevailing at that time, marijuana smokers then ingested, on average, only one-third as much THC as present-day marijuana smokers in the United States.

7. Cannabis-induced delirium (acute confusional state)

Summary of Chapter 7

Cannabis smoking can cause an acute and short-lasting (between a few hours and a few days) state of profound delirium. The individuals affected experience complete or partial loss of their orientation ability, their memory and their sense of their own identity. An element of delirium is a common occurrence in cannabis-induced psychosis.

This condition is probably more likely to arise if high doses of THC are involved or if the individual is in a weakened condition, for example owing to lack of sleep or to withdrawal symptoms relating to alcohol or other drugs.

Certain experts have calculated that delirium or cannabis-induced psychosis occurs at one time or another in 10 per cent of all cannabis abusers.

There is widespread agreement that the use of cannabis, especially in high doses, can cause delirium (Hollister, 1986; Negrete, 1983; Tunving, 1985; Thornicroft, 1990; Chaudry et al., 1991), which is also known as acute confusional states. This is a short-lived condition, lasting from a few hours up to a few days. One characteristic of this condition is unclear consciousness: the persons affected have difficulty with spatial and temporal orientation, are unable to correctly perceive the situation in which they find themselves, and may fail to recognise close acquaintances. Not infrequently, this condition is difficult to distinguish from cannabis-induced psychosis, which is described in the next chapter. It is likely that conditions are often encountered which are a mix of delirium and cannabis-induced psychosis. Castle and Ames (1996) designate all transient confusional states, "cannabis psychoses" and psychosis-like conditions as "acute brain syndromes" (or "encephalopathies").

The main feature is profound confusion with regard to space, time, place and the people nearby, as well as uncertainty with regard to one's own identity. Misjudgements of sensory impressions and memory disturbance may also occur, as well as language disturbances (such as incoherent speech). Dramatic and rapid shifts in the person's mental state are not unusual. There may also appear, in varying degrees, genuinely psychotic symptoms such as delusions and hallucinations.

In all probability, the THC strength of the cannabis preparation used is important to whether or not the condition is provoked. Holister (1986) is one of the researchers who believe that this is why cannabis-induced delirium was significantly more common outside Canada and the United States (such as Sweden) in the mid-1980s, since hashish was more common than marijuana in these countries at the time, and hashish is a stronger type of preparation. Hashish remains more common in these parts of the world, while marijuana is dominant in North America.

The condition is probably more likely to be provoked in persons who are in a physically weakened state for a variety of reasons, such as physical illness, malnourishment, severe sleeplessness, the effects of other drugs or withdrawal symptoms.
The symptoms are frightening both to the individual and to those who witness them. Since a completely disoriented person may sometimes perform actions which are based on a totally erroneous perception of the surrounding reality, the condition can be serious and place the individual in dangerous – on occasion even fatal – situations. Under the heading "Cannabis and suicide", I account for a Swedish study of deaths caused by jumping from a height while under the influence of cannabis. In at least one of the cases reported, I have been able to conclude, by examining medical records, police reports and other material, that the suicide was carried out under the influence of severe disorientation/confusion, even though a (non-depressive) psychosis was present at the same time.

As has previously been mentioned, it is very difficult to calculate how common it is that cannabis abusers are affected by a given harmful effect. However, cannabis-induced psychosis/delirium appears to be a common side-effect based on clinical experience and reports from cannabis abusers and their relatives. Please refer to the next chapter, which deals with cannabis-induced psychoses.

8. Cannabis-induced psychosis

Summary of Chapter 8

Cannabis smoking, especially of preparations with an high concentration of THC, can cause a toxic and short-lived psychosis (between a few days and a few weeks). Not infrequently, this psychosis has dramatic symptoms and may require hospitalisation, sometimes under constraint. Elements of delirium are common.

If the individual concerned stops smoking, the condition probably has a good prognosis. If he or she continues to smoke cannabis, however, the psychotic condition can probably remain for a long time. It can be difficult to distinguish cannabis-induced psychosis from schizophrenia.

Different assessments and calculations of how common this side-effect is have yielded similar results. As a "rule of thumb" it is considered that, on average, a person who smokes cannabis runs a 10 per cent risk of being affected at one time or another by cannabis-induced psychosis or delirium.

A Danish retrospective, long-term follow-up of more than 500 short-term "cannabis-induced psychoses" showed that 44.5 per cent had a psychosis within the schizophrenic spectrum. Refer to the chapter on "Cannabis smoking and schizophrenia".

Toxic cannabis-caused short-lived psychosis can sometimes be difficult to distinguish from the toxic cannabis-induced delirium described above and sometimes the conditions merge. What primarily distinguishes the delirium from the psychosis is the degree of the clouding of the consciousness. In the psychotic condition, the clouding of the consciousness is just a component among the otherwise psychotic symptoms. Since the psychosis often lasts longer (one to six weeks) than the actual intoxication, one can expect to find a delayed toxic effect. The mechanism behind this progression is unknown. This progression in time presupposes that cannabis smoking has ended. If the person continues to smoke cannabis, the psychotic condition, which otherwise responds very well to treatment, is likely to continue for a very long time.

It is sometimes very difficult to distinguish cannabis-induced psychosis from acute schizophrenia. However, some researchers maintain that the typical picture of cannabis-induced psychosis does differ from that of schizophrenia and is characterised above all by what are known as "positive" symptoms such as paranoia and other delusions, hallucinations and, not rarely, affective (emotional) changes where aggressiveness alternates with euphoria. What otherwise distinguishes these conditions from acute schizophrenia is in part that a cannabis-induced psychosis results in clouding of the consciousness while not disrupting thought, which is present in the majority of schizophrenic patients (Thacore & Shukla, 1976). However, what

mainly distinguishes them lies in the subsequent course taken by the condition: cannabis-induced psychosis is short-lived, while by definition the course of schizophrenia lasts for at least six months (according to the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV]).
Schizophrenia is sometimes associated with a "premorbid personality" (i.e. it expresses itself prior to onset of the illness), which can manifest itself in various forms. This commonly includes extreme seclusion, loss of earlier interests, vague delusions such as suspiciousness, and bizarre ideas.

However, some of these symptoms may be typical in a chronic hashish smoker, and it may be difficult to distinguish these diagnoses. If there are no hereditary factors for schizophrenia, the likelihood of the diagnosis as cannabis-induced psychosis increases. Accordingly, the most certain way of distinguishing between the two kinds of psychoses is to monitor the course taken by the psychosis. If the person stops taking cannabis (as well as any other hallucinogenic or CNS stimulant drugs), cannabis-induced psychosis is short-lived. However, if the person continues to smoke hashish or marijuana, thus ensuring the persistence of the psychosis, it may sometimes be difficult to distinguish the condition from schizophrenia or another potential functional psychosis.

Like the delirium described above, an outbreak of cannabis-induced psychosis is often frightening to the individual concerned and to his or her family. Although this condition has a good prognosis and a generally short-lived progression from a psychiatric point of view, it still must be considered a very serious condition. It often requires hospital treatment, not rarely involving hospitalisation under restraint, and during the intensive phase of the psychosis there is probably an increased risk of suicide, for instance by jumping from a height (see the section on depression and suicide in Chapter 11). Even where the course taken by the psychosis is not dramatic, the subjective view is that the condition represents a temporary mental breakdown, and this is an experience which can cast a shadow over a large part of the person's future life.

Scientific and clinical reports

There are differing opinions in the scientific literature as to whether or not cannabis-induced psychosis exists. In several cases, there has in fact been a mix-up with the delirium described above – a mix-up which is understandable since the conditions sometimes tend to follow similar courses (Thornicroft, 1990). Most researchers, however, are of the opinion that the phenomenon as such – a toxically provoked psychotic reaction – does exist, and *cannabis-induced psychotic disorder* is indeed included as a diagnostic unit in DSM-IV.

To complicate matters still further: in several research reports, especially older ones, "cannabis psychosis" refers to a more long-term, functional and non-toxic (except possibly in the initial stages) condition. This means that, in many cases, the lack of agreement has related to a condition other than the one I have described here.

There is a large body of reports from researchers who have themselves studied cases of cannabis-induced psychoses (sometimes called cannabis psychoses and sometimes hashish psychoses) or collected case descriptions from clinicians: Bernardsson & Gunne, 1972; Pålsson, Thulin, Tunving, 1982; Tunving, 1985; Carney, 1984; Brook, 1984, to name a few slightly older descriptions. As the existence of this type of psychosis has been gaining acceptance, at least in the Nordic countries (Kristensen, 1994), such reports have become rarer, while the question of whether cannabis can cause chronic psychosis has come more to the fore. In the United Kingdom, however, where there has been more debate on whether cannabis is dangerous at all, a number of reports on cannabis psychosis have been published, such as Wylie, 1995 and McBride & Thomas, 1995. Both of these reports mention habitual smokers having developed delirious and/or psychotic reactions after smoking high-dose preparations.

There are scientific studies that are methodologically more advanced that indicate the existence of these psychoses and make comparisons with control groups of patients not affected by cannabis. The studies by Rottanburg, et al. (1982) and Rolfe, et al. (1993) should be mentioned above all. Chopra, et al. (1974) have also contributed extensive knowledge of cannabis-induced psychoses in a large-scale study. On the basis of in-depth analyses of published research findings, Ghodse (1986) and Thornicroft (1990) conclude that cannabis can provoke toxic psychoses, especially when the THC concentration is high.

An example from the author's own clinical work:

> While I was collecting material for the first version of the present report, I was also professionally active in a private general psychiatric practice. A young patient (23 years old) was referred to me. He displayed the full range of signs described above: no history of mental illness, no divergent personality traits prior to this disturbance and no schizophrenia in close relatives. This patient's illness had developed after a period of intensive cannabis smoking. He suffered from pronounced paranoia, "magical" imaginings, pronounced suspiciousness and impulsive outbreaks involving aggressiveness towards members of his family as well as severe sleeplessness (being awake all through the night). By organising round-the-clock care and supervision within his family, making sure he saw me frequently and could phone me at more or less any time of the day or night, and quickly starting treatment with antipsychotic medication, it was possible to avoid having him admitted to a hospital. The psychotic symptoms proper faded after 7–10 days, after which there followed a convalescence period lasting for a couple of months, as well as a few relapses.

Some recent studies

Two teams of researchers (Núñez et al., 2002; Basu et al., 1999) have been able to confirm previous findings where a distinction, based on several features, had been drawn between two different groups of psychoses: acute schizophrenia on the one hand and short-lived toxic psychosis – cannabis-induced psychosis – on the other.

How common is cannabis-induced psychosis?

How common, then, is cannabis psychosis? We do not know for certain. There is probably some degree of underdiagnosis. Most studies from around the world show that there is a tendency at general psychiatric clinics to underestimate the patients' drug abuse (including alcohol abuse). It is a well-known fact at locked psychiatric wards and prisons that it is well-nigh impossible to keep the institution free from drugs. The situation looks differently only at specialised clinics and some special prison wards.

It is probably not unusual for patients to continue abusing cannabis (unbeknownst to the staff) even when they have been admitted to a hospital, which can give rise to a longer-lived, schizophrenia-like course of illness. In such cases, the wrong diagnosis can be made. Another reason why the recorded diagnosis may not be cannabis-induced psychosis is that poly-drug abuse is extremely common. If the individual concerned has been using, for instance, both cannabis and CNS stimulants – a frequent combination in Sweden – we can no longer talk about a pure cannabis-induced psychosis, and the diagnosis is usually determined by the other abuse. Sometimes the condition can be dealt with in outpatient psychiatric care, and then – in Sweden at least – no note at all is made of the diagnosis in any central register.

For the above reasons, then, it is a difficult task to estimate the prevalence of cannabis psychosis. One must after all distinguish cannabis psychosis from "psychotic symptoms" (serious enough, but not sufficient to warrant classification as a true illness) on one hand and acute schizophrenia on the other. However, several attempts have been made at both estimating and measuring the frequency of cannabis psychosis.

Based on long experience and a literature review, Johnson (1991) estimated that 10 percent of all those who had used cannabis on more than a single occasion was afflicted by a cannabis psychosis or delirium. This figure seemed high at the time, but later assessments have confirmed rather than refuted it. The most interesting study may be that carried out by Thomas (1996), who sent questionnaires to 1,000 New Zealanders aged 18–35 years, receiving a reply from 65 per cent. Of these, just under 40 per cent had used cannabis; and of these, 15 per cent had experienced psychotic symptoms. The now commonly accepted rule of thumb is that *10 per cent of those who smoke cannabis risk being affected by psychotic symptoms, which in many cases will amount to a proper cannabis-induced psychosis*. Johns (2001) also supports this assessment. However, here it must be pointed out that, in Thomas' study in particular, there is a shift between cannabis psychosis and "psychotic symptoms", which must be considered as an undesirable and frightening, although not

entirely uncommon effect of the normal intoxication. It is most often triggered by higher doses and individual conditions of the smoker.

In a British report (Wylie et al., 1995) describing observations of a wave of psychosis and confusional states, it is emphasized that these observations were made in a group of abusers consuming Dutch cannabis with a very high THC content. In other words, the risk quantified above becomes greater if the individual concerned uses preparations with a higher THC concentration, which has previously been pointed out by many others.

Prognosis, the association between cannabis-induced psychosis and schizophrenia/schizophreniform psychosis

As can be seen, there are a number of studies on how common cannabis psychosis is and what the typical signs are. In spite of this, the study of the condition is far from complete. The majority of the studies are more of a nature of case studies and there is a lack of long-term follow-ups.

The prognosis of cannabis-induced psychosis is good on condition that the abuse ends, but this may only be true on the short term. At the end of Chapter 9 on cannabis smoking and schizophrenia, a Danish study is presented which shows in a multi-year follow-up that cannabis-induced psychosis can predict schizophrenia, schizophreniform psychosis or other, more short-lived psychotic conditions (not directly cannabis induced). Of those diagnosed with "cannabis-induced psychosis", 57 per cent were found by the Danish study to have been afflicted later by a functional psychosis. The role that continued or resumed abuse plays in such a dire outcome is unknown.

9. Cannabis smoking, schizophrenia and schizophreniform psychoses

Summary of Chapter 9

There is a causal relationship between cannabis smoking and the onset of schizophrenia.

After a closer review of the Swedish conscript study from 1987 and its 27-year follow-up from 2002, four reviews are presented that indicate consensus over a dozen studies from the 2000s.

The various studies show that the risk of having a "psychotic outcome" (lasting psychotic symptoms – after the cessation of abuse, onset of non-specific psychotic illness or the onset of schizophrenic disorders) is 2-3 times greater with cannabis smoking. When a difference in the total dose was documented, it was found, with regard to schizophrenia, that the risk was higher, the higher the total registered does was.

All of the authors of the reviews referred to seek societal intervention to reduce cannabis abuse and thereby reduce the risk of psychoses among young people.

What effect does cannabis have on schizophrenia that has already presented itself?

It is well known among clinicians that cannabis smoking interacts with manifest schizophrenia: cannabis smokers experience more relapses (more frequent hospitalisation), their symptoms are more dramatic, and they are less susceptible to the effects of neuroleptic medication. In one section, studies are presented where an attempt was made to understand the dynamics of such – often destructive – self medication.

Among the most serious harmful effects of cannabis are those of co-morbidity between cannabis and schizophrenia, especially if consideration is also taken of the interaction between cannabis and the vulnerable individual that results in a schizophrenic disorder.

Cannabis smoking and schizophrenia – is there a causal relationship?

Several of the findings from the aforementioned studies (e.g. Holmberg, 1981; Bier & Haastrup, 1985; Tennant & Groesbeck, 1972) suggest that there may be a *connection* between cannabis smoking and psychosis. Strictly speaking, all of previously mentioned studies indicate such a connection, with exception for conditions categorised as delirium. When illness has been more prolonged, schizophreniform psychosis may be suspected. However, no certain conclusion can be drawn regarding a causal relationship based on these studies, since they do not fulfil the methodological requirements to do so.

As early as the beginning of the 1970s, Breakey et al. (1974) pointed out that there was some form of association between drug abuse (including cannabis abuse) and the onset of schizophrenic illness. He considered that cannabis precipitated latent schizophrenia, but also believed that there were grounds for suspecting that cannabis could precipitate schizophrenia in cases where the illness would otherwise not have become manifest. The reasons were that the onset of drug-induced schizophrenia occurred on average four years earlier than the onset of other forms of schizophrenia, that the onset was more sudden than in other schizophrenics, and that the patients' personality before the onset of the illness was consistently better than in a comparable group with non-drug-induced schizophrenia. Hereditary aspects were not touched upon in this study. Eikmeier (1991) arrived at similar results with regard to age at onset 20 years later in a larger-scale study which looked only at cannabis-induced schizophrenic psychoses as compared with drug-free schizophrenic psychoses. A few later studies show the same findings (Veen et al 2004, Arendt et al 2005).

These studies indicate that cannabis has its "own" effect, but it does not prove that cannabis use causes schizophrenia. They do, however, indicate that the people affected become ill earlier and present a different clinical picture.

In the following chapter, I will present three aspects of the co-morbidity between cannabis use and schizophrenia. All three provide support for there being a connection between cannabis and schizophrenic psychosis.

1. Cohort studies on the *causal relationship*.
2. Effect of cannabis on established schizophrenia.
3. A study of the likely connection between cannabis-induced, short-term, toxic psychoses and later development of schizophrenia.

Cohort studies

Well-done cohort studies are the main scientific method for answering the question of whether cannabis can trigger/cause schizophrenia. It is a prospective, long-term study that covers a population that is not too small. The population should be as representative as possible of the general population or include a randomly selected sample of a special group that is particularly important to study. However, very special groups such as patients in healthcare are usually avoided even though they are easier to contact than others.

To establish a clear causal relationship, three base criteria must be met:

- *There must be some type of connection between the "cause" (exposure) and the disease, for example that schizophrenia manifests itself more often among cannabis abusers than other comparable individuals.*

- *The cause and the results (the schizophrenic illness) must have a temporal relationship that makes a causal relationship possible, in other words, the abuse must appear before the disease.*
- *Change connection. The cause must make a difference, i.e. cause a change in the outcome. The most common way of seeing this is that the outcome (in this case, the disease) appears more often among those who smoked cannabis than among others (comparable).*

When assessing the risk that a psychosis will manifest itself in a cannabis-exposed group, if the risk is found to regularly increase with more intensive abuse, this constitutes a strong support for the change connection and for the causal relationship in general.

The strength of the third factor is corrected by a control for so-called covariant factors. The strength of the evidence also increases if there is some theoretical, biologically feasible explanation. However, it is most important that the findings – the causal relationship – are replicated in other well-implemented cohort studies (M Susser 1991).

A major and methodologically high-quality cohort study was not presented until 1987. It was Andréasson's, Allebeck's, Engström's och Rydberg's (1987) large follow-up of 50,000 Swedish conscripts. The researchers compared information from the enrolment of the conscripts (1970), including data concerning drug habits, with registered schizophrenia diagnoses at Swedish hospitals during the ensuing 15-year period. They also had the opportunity to gather in a large amount of other data from the very comprehensive enrolment procedure. This included access to information on current and previous state of health, social conditions and so on.

It was found that a person who had claimed, at the age of 19, to have consumed a great deal of cannabis (on more than 50 occasions) was six times more likely to be diagnosed as schizophrenic during the subsequent 15-year period than a person who had claimed at enrolment that he had never used cannabis at all. When account was also taken of other covariant factors known at the time of enrolment which could increase the statistical likelihood of being diagnosed with schizophrenia, the cannabis-dependent risk became smaller, but there remained a statistically significant increase in risk. Those who had smoked once or more ran a 2.4 times higher risk of being afflicted by schizophrenia compared with those who did not smoke at all.

On publication, this study justifiably aroused considerable attention, and it has probably been the most frequently cited study in the international research literature on the relationship between cannabis and psychosis. Reactions to it ranged from total acceptance (Ottosson, 1992) to extensive criticism (Johnson et al., 1988). Negrete – the doyen of this field – judged the connection between cannabis and the precipitation of latent schizophrenia to be reasonable, on the basis of this study as well as previous ones (Negrete, 1989). At the same time, though, he was of the

opinion that the study suffered from a number of weaknesses. A decisive majority believe, however, that this study was the first that showed a causal relationship between cannabis smoking and schizophrenic illness. The increase in risk was also dose dependent, meaning the more cannabis they had used, the higher the risk was. Andréasson et al. (1989) och Allebeck et al. (1993) have carried out a couple of supplementary studies in which they have tried, in large part successfully, to eliminate the weak points of the original study and strengthen their original findings. The latter study involved going through information from the medical records of more than 112 patients in the county of Stockholm who had been diagnosed with both schizophrenia and cannabis dependence. The researchers looked at such aspects as the clinical picture at the onset of illness, the temporal relationship between the cannabis abuse and the onset, and the potential involvement of other drugs, above all amphetamine. In all significant respects, the findings which were made in these studies confirmed the conclusions reached in the original study.

Further support as regards one aspect of that study comes from an examination of 100 randomly chosen medical records of patients diagnosed as having schizophrenia in the period 1973–1977. The researchers found a large degree of consistency across regions and hospitals as well as over time, and also a large degree of conformity with the DSM-IV diagnostic criteria for schizophrenia (Dalman et al., 2002).

In the original Swedish study, the first analysis was performed 15 years after the enrolment of the conscripts. In order to add further strength to their findings and to extend the study, a follow-up analysis was performed 27 years after the time of enrolment. The research group now comprised Swedish and British researchers (Zammit et al 2002). By comparing the group of people who had fallen ill within five years of enrolment with those who had fallen ill later, and by re-analysing the data provided at the enrolment interviews – in the light of 12 more years' worth of research into the importance of various background factors in the development of schizophrenia –, the researchers were able to dismiss a few of the objections which had been made to the original study. The risk of falling ill with schizophrenia was approximately the same for those who had fallen ill within five years as for those who had fallen ill later. It was thereby possible to refute the suspicion of not having paid attention to people with prodromal phase schizophrenia, in other words those with signs of a upcoming outbreak of schizophrenia (who would have taken cannabis as self-medication). An extended control for covariant factors was also done. None of this changed the results.

Cohort studies in the 2000s

It was not until the 2000s that more cohort studies were presented that can supplement and support the Swedish and the Swedish-British studies of the Swedish conscripts.

A surprisingly large number of long-term cohort studies have been published that investigate whether cannabis precipitates/causes *schizophrenia*, other *psychoses* or

psychotic symptoms. Experienced researchers have also reviewed the methodologically best studies among these in surveying articles. From seven to nine reviews, I have picked out four that reviewed a selection of these studies, which in part were the same studies in the various reviews. I will present their conclusions as briefly as possible. An interesting observation is that approximately the same increase in risk is found in these studies, regardless of which of the three "psychotic" outcomes were focused on. Regardless of outcome, cannabis smokers had a risk of being afflicted that was two to three times higher than the non-smoker. The risk increase for the outcome of schizophrenia was also found to be directly related to the total dose of cannabis.

The reviews:

Louise Arsenault et al: Causal association between cannabis and psychosis: examination of the evidence (2004) (four studies).

Conclusion*:"Cases of psychotic disorder could be prevented by discouraging cannabis use among vulnerable youths. Research is needed to understand the mechanisms by which cannabis causes psychosis."*

Filip Smit et al: Cannabis use and the risk of later schizophrenia: a review (2004) (five studies).

Conclusion: *"Antecedent cannabis use appears to act as a risk factor in the onset of schizophrenia, especially in vulnerable people, but also in people without prior history. There is an intrinsic message here for public health, but how that message is to be translated in to action is not immediately clear."*

Louisa Degenhardt and Wayne Hall: Is cannabis use a contributory cause of psychosis? (2006a, 2006b) (six studies).

Conclusion*: "It is most plausible that cannabis use precipitates schizophrenia in individuals who are vulnerable because of a personal or family history of schizophrenia." In a companion paper the authors add: "We should discourage young adults seeking treatment in mental health services from using cannabis and inform them of the probable mental health risks of cannabis use, especially of early and frequent use. We must exercise caution in liberalizing cannabis laws in ways that may increase young individuals' access to cannabis, decrease their age of first use, or increase their frequency of cannabis use. We should consider the feasibility of reducing the availability of high-potency cannabis products."*

Theresa HM Moore, Stanley Sammit et al: Cannabis use and risk of psychotic and mental health outcomes: a systematic review (2007) (11 studies).

Conclusion*: "The evidence is consistent with the view that cannabis increases risk of psychotic outcomes independently of confounding and transient intoxication effects, although evidence for affective outcomes is less strong. […] However, we*

conclude that there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life."

In total, this involved ten studies that were originally presented in some 15 articles and then reviewed in seven to eight reviews. The reviews not selected have largely discussed the same studies and arrived at similar results. The exception to this is a review by Macleod et al (2004), where the associations are difficult to survey due to a very broad allocation for the outcome "psychosocial problems" (T. Moore et al 2007). Macleod also applies a view of observational studies of this type that in practice means that the cohort study cannot provide strong evidence of there being a causal relationship, regardless of how methodologically well-done the study is. These opinions have been addressed and refuted by de Irala et al (2005) and Peter Allebeck (2004), among others.

> The cohort studies and the four reviews provide very strong scientific support for cannabis being able to induce schizophrenia in vulnerable individuals, as well as strong support for cannabis being able to cause schizophrenia.

Cannabis and schizophrenia at a public health level

Several of the aforementioned researchers are of the opinion that the number of schizophrenics in society would decrease if cannabis smoking decreased. Some support calculations of the proportion of schizophrenics in a certain society that could be avoided if cannabis smoking disappeared. Arsenault et al believe that this "aetiological fraction" for New Zealand is 8 per cent and Moore's group support the figure of 14 per cent for the United Kingdom.

One argument against cannabis being able to cause schizophrenia (which would not have manifested itself otherwise) is that the incidence of schizophrenia in, for example, the U.S. decreased or remained constant during the 1970s and 1980s (e.g. Hall and Pacula 2003), at the same time that cannabis abuse grew. The same is true of the European countries. Calculating the incidence of schizophrenia is very complicated, however, (Kendel et al 1993), especially during a period of major economic and cultural shifts, considerable migration and, not least, changes in the diagnosis criteria for schizophrenia in several countries.

In addition, two studies have been published in Europe in recent years regarding the changes in the incidence of schizophrenia in high cannabis consumption areas.

Ajdacic-Gross et al (2002) investigated the incidence (frequency of new cases) of schizophrenia in the Swiss canton of Zürich during the period 1977-2005. Over nearly two decades, the incidence was unchanged among men and declining somewhat among women. This trend turned during the second half of the 1990s. The youngest age group (15-19 years) showed a strong increase in the number of those who fell ill with schizophrenia/schizophreniform psychosis. The largest increase was

observed in men. For some time, it doubled. In the beginning of the 1990s, cannabis use increased among 15-16 year-olds. Those who had "ever used" amounted to 15 per cent among boys and 5 per cent among girls in 1990, whereas in 1998 these figures were 41 per cent and 30 per cent, respectively, and in 2002 they were 50 per cent and 39 per cent, respectively.

In an initial study, Boydell, van Os, et al (2003) showed how the incidence of schizophrenia doubled in southeast London between 1965 and 1997. In a later study (Boydell, van Os et al 2006), the same research group showed how the proportion with schizophrenia, the onset of which was preceded by and probably caused by cannabis use, increased strongly during the period.

> All of the authors of the reviews express a view that society needs to take action, including providing information to reduce cannabis abuse, especially among younger people, and thereby decrease the risk that adolescents and young adults are afflicted by psychoses.

How does cannabis affect already established schizophrenia?

In healthcare and addict treatment, it has long been noted that the clinical picture of schizophrenics is affected by the patient smoking or consuming cannabis otherwise. Attempts have also been made at shedding light on this area through straightforward research. However, the latter has been done on a somewhat modest scale relative to the problems that schizophrenia combined with cannabis use causes for the patients and psychiatric care.

According to Negrete et al. (1986), the interaction between cannabis smoking and schizophrenia has the following characteristics: cannabis smokers experience more relapses (more frequent hospitalisation), their ("positive") symptoms are more dramatic, and they are less susceptible to the effects of neuroleptic medication (which inhibits the nervous system). In a six month long comparison of cannabis smokers and those who did not, Negrete found that smoking was one of the most powerful external negative factors. It often was of greater significance than the stage of the disease, the patient's age and temporary use of other drugs as well as the dose of antipsychotic medication. The effects seem to be dose-dependent (Linszen, 1995).

D.A. Treffert (1974) studied the progression in four schizophrenic patients. They were on antipsychotic medication and all four occasionally smoked cannabis, despite being warned. Their condition regularly worsened during periods of cannabis smoking, and improved during breaks in use. The degradations were regular and sometimes dramatic with dangerous complications. Stable remission only took place when the patients stopped smoking. In spite of the few cases, Treffert's detailed documentation constitutes an important illustration that can be recommended to those who encounter these, often very complicated, cases in healthcare.

Over the years, many psychiatrists have found themselves able to make similar observations: cannabis smoking causes a deterioration regardless of antipsychotic medication.

These various aspects of the interaction between cannabis and schizophrenia were later demonstrated in a number of studies (Gray och Thomas 1996. Bersani, et al., 2002; Caspari, 1999). Degenhardt and Hall address these problems in a review (2001).

Why do schizophrenia patients smoke cannabis?

In societies where cannabis is readily available, there is a high degree of co-morbidity between cannabis abuse/dependence and schizophrenia. Clinicians, researchers and relatives have often asked the question of why such a high proportion of schizophrenic patients use cannabis even though they objectively so often get worse from smoking.

Of course, many have wondered whether there are any symptoms of the illness or negative effects from the medication that the patients have tried to "self medicate" with cannabis. Peralta V. and Cuesta M.J. (1992) studied 95 schizophrenic patients under treatment. Of those, 23 patients had smoked cannabis at a level corresponding to abuse during the past year. In a comparison of how the mental illness manifested itself, it was found that the psychotic patients that were also cannabis smokers had significantly fewer negative symptoms. The authors believed that the most likely explanation was that the 23 patients had self-medicated themselves to address some of the negative symptoms (such as indifference and sleeping disorders).

Schofield et al (2006) interviewed 49 patients diagnosed with schizophrenia or schizophreniform psychosis. All of them had used cannabis in the past six months. The intent was to use interview forms to obtain a perception of what amounts of cannabis had been consumed and, above all, what symptoms/discomfort that patients wanted to moderate with the intake of cannabis. In addition, they tried to achieve some clarity as to whether it was a matter of "self-medication" against a) symptoms from the main disease, b) symptoms from another disease such as depression, or c) side-effects of medication.

The researchers were aware that it could be difficult for both the patients and the interviewers to distinguish the origins of the symptoms as well as the effects of cannabis, among other factors. However, they believed they could see a dominant pattern where the following problems were given as the primary reasons for the cannabis intake:

- weariness (one of the most common symptoms in prior studies)
- difficulties finding friends
- sleeping difficulties.

Other problems:

- symptoms of anxiety:
  - inner unease/agitation
  - sleeping difficulties
  - muscle tension
  - shakes
  - nightmares.

These symptoms can all be expressions of psychoses, anxiety syndrome, depression or (most like) side-effects of antipsychotic medication.

- Problems that are probably expressions of negative schizophrenic symptoms:
  - feelings of depression
  - lack of feelings, emotions for others
  - fatigue, lack of energy
  - sleepiness/drowsiness.

These can also be side-effects of medication.

The important factor for clinicians who want to help the patient from getting worse and committed is to clarify the patient's symptoms and try to remove these reasons for taking cannabis. This is the researchers' conclusion.

Many are likely to feel uncertain as to how to be able to follow the advice of researchers. In connection with a query similar to than of Schofield's study above, W.F. Costain (2008) uses a qualitative method. The results provide a comprehensive view of the schizophrenic patient's self-image and view of the surroundings, including the view of smoking cannabis. This understanding of the patient's phenomenological interpretation of the world may seem to turn the "regular" clinical method upside down, but provides the author a basis for the development of a therapeutic relationship where the doctor obtains a completely different chance of influencing the patient.

The group studied comprised 30 patients, several of whom had a history of many years of illness and all of whom were diagnosed with schizophrenia (according to DSM IV). Somewhat less than half of them were treated with outpatient care and the rest were institutionalised. All patients were interviewed by the same researcher. A relative or close friend of the patient, who was chosen by the patient him or herself, was also interviewed. Costain tried to understand the patient's subjective perceptions of his or her situation and relationship with the disease and cannabis smoking, and arrived at the following conclusions, among others:

- The majority of the participants in the study did not realise that they had a psychotic illness and they had a strong belief in the usability and benefits of cannabis. This also included nuances where certain phenomena were recognised as expressions for a psychotic or other mental illness.
- Many felt that their condition was an expression for a spiritual awareness, an awareness that in many cases was amplified by cannabis – frightening to some, but also positive to many.
- The positive symptoms were reinforced in a positive manner. This applied especially to voices and hallucinations, which became higher and clearer or more intensive.
- At the same time, cannabis increased the person's possibility of controlling these symptoms.
- Cannabis made them feel more normal, allowed them to feel less mental anguish, provided more energy and permitted a perception of improved cognitive functioning. The patients felt that they gained a greater clarity of thought and more creativity.

The researchers believe that these opinions from the patients expands the understanding previously obtained from the quantitative studies (including Schofield's study). In a concentrated review, it is difficult to do the text justice since the text itself is not entirely simple. It is important to emphasize that the researchers assert the importance of accepting the patient's view of him or herself and the world as his or her reality. They encourage to not dissect it or encourage it, but to accept the patient's view of the world as the starting point for a (therapeutic) meeting.

Is cannabis-induced psychosis a precursor of schizophrenia or schizophreniform illness?

Most of the descriptions of what I refer to here as cannabis-induced psychosis (short-term, likely toxic psychosis) have almost entirely been provided in the form of case studies. These studies have also been characterised by a lack of any longer follow-ups. Even when the patients have not recovered as fast as usual, due to earlier psychotic tendencies, the patient has responded to medication and the case was left. No group of this type of patients has been monitored for more than three months (M. Arendt et al 2005).

Mikkel Arendt et al conducted a retrospective follow-up of 535 patients diagnosed with *cannabis-induced psychosis* (code F12.5 in ICD 10) who were treated at Danish psychiatric clinics (in outpatient or institutional care) during the period 1 January 1994 to 15 July 1999. Only one symptom manual was used in Denmark at the time, ICD 10, and F12.5 is a good match for how we have defined cannabis-induced psychosis in this report. The manual also provides space for other closely related diagnoses. The study group only included patients who were treated for

cannabis-induced psychosis for the first time. Those whose background included another psychotic illness or bipolar disorder were also excluded. The follow-up was concluded on 1 July 2002 with an average follow-up period of 5.9 years (3-8.5 years).

The researchers followed the study group's continued contact with healthcare. With a follow-up time as per above, they found that 44.5 per cent eventually developed a psychotic illness in the schizophrenic spectrum (schizophrenia, schizotypal disorder or schizoaffective disorder), possibly through one or more relapses in short-term cannabis-induced psychosis. A proportion amounting to 12.5 per cent were afflicted by some other, non-acute drug-induced psychotic condition.

It is interesting to know the age at which people fall ill with schizophrenia spectrum disorders. The researchers therefore compared data with 2,721 patients who had fallen ill with schizophrenia the first time in 2002 or 2003 without having used cannabis. The men in the cannabis psychosis group were then found to be between 2.2 and 7.2 years younger than the cannabis-free group. They differed to varying degrees depending on what type of schizophrenia they had. Among the women in the cannabis-psychosis group, only those with paranoid schizophrenia were younger (3.1 years) than the women of the control group at the time of onset.

A retrospective study without medical record controls, without controls for cannabis and other drugs during the follow-up period and without information on special vulnerability in the study group can probably not be the basis of definitive statements on a causal relationship. The lower age at onset provides some support, however, to cannabis at least having been a partial causal factor. It is a known phenomenon that cannabis accelerates the schizophrenic illness process (W.R. Breakey et al 1974, N. D. Veen et. al 2004).

It is likely that Arendt's study group comprises a negative selection of severe cases. Short-term cases and cases with a less dramatic profile and milder psychotic symptoms probably never found their way into the healthcare system and probably had a more positive prognosis.

In summary, there is reason, however, to view cannabis-induced psychoses as risk factors for a later development of schizophreniform psychotic conditions, or other serious mental illnesses. If the person stops abusing cannabis, the risk probably decreases that he or she will develop a functional psychosis.

It is very important that prospective studies be conducted where the long-term progression after a toxic *cannabis induced psychosis* is studied further.

10. Anxiety conditions and depersonalisation syndrome

Summary of Chapter 10

Cannabis intoxication can induce anxiety attacks of varying strength. Such attacks of panic anxiety are probably a relatively frequent side-effect. They are believed to be more common in occasional smokers or smokers who ingest a larger amount of THC than they are used to.

Further, the anxiety attack may signal the beginning of a protracted panic-anxiety syndrome which does not differ from panic-anxiety illness that begins in some other way. Cannabis smoking can also provoke a relapse into panic-anxiety syndrome.

On occasion, experiences of unreality, which are a common feature of cannabis intoxication, may become so strong that they dominate the experience of intoxication. These anxiety-like "depersonalisation syndromes" generally abate rapidly after intoxication. There are, however, a number of published case studies where the feelings of unreality have persisted over a very long period after being provoked. In some cases, the symptoms have had a debilitating effect and have been very difficult to treat.

In a survey of 117 patients with chronic/long-lived depersonalisation syndrome, cannabis was found to be the third most frequent provoking factor.

Anxiety conditions

One of the contradictory characteristics of cannabis is that it can both relieve anxiety and give rise to pronounced attacks of anxiety and panic. Such anxiety attacks are probably the most common side-effect experienced by smokers of cannabis (Hollister, 1986; Mathew et al., 1993), and most cannabis smokers have themselves had them or seen their friends affected by them. This is a well-known phenomenon in abuser circles, but it has also been demonstrated under experimental conditions (Sheehan & Sheehan, 1982). In a survey of 200 cannabis abusers, 22 per cent stated that they had experienced panic anxiety on at least one occasion (Thomas, 1996).

While the condition is more frequent in beginners, it also occurs in more experienced users. This side-effect depends on many factors, but the cannabis dose is probably the most important. However, here it is not a simple linear dose dependence, but rather the difference in effect usually attributed to THC's *biphasic effect curve* (see chapter 2). In lower doses, it provides reduced anxiety, calm and euphoria and less depressiveness. On the other hand, in higher doses, it results in anxiety, panic, paranoia and other psychotic symptoms. The individual's risk of having anxiety reactions also increases in other circumstances: if the person is a beginner, has had anxiety reactions before or is mentally vulnerable in another way.

These panic anxiety attacks can be very frightening, with a strong feeling of losing control, going mad, and so on. Nevertheless, those affected seldom seek professional help – instead, the situation is dealt with within their circle of friends. The condition is generally short-lived, its only consequence being that the persons affected are subsequently more careful with doses and with the social setting in which they smoke, or that they stop using the drug completely.

Accordingly, there is no doubt that cannabis relatively often causes acute, temporary anxiety attacks. The question of whether the influence of cannabis can also initiate a panic-anxiety syndrome or other anxiety disorder is important, but more difficult to answer. Firstly, it is often difficult to delimit the anxiety disorders from "normal" unease. Other conditions that complicate the assessment include the fact that anxiety is often associated with the intoxication. Anxiety appears – as described above – like a part of the intoxication, but is also a common component of the withdrawal phase. Low doses of THC may possibly mitigate anxiety, and attempts at self-medication probably occur.

In a cross-sectional study that covered 4,745 adults (the study was a part of the larger Colorado Social Health Survey), Zvolensky et al (2005) showed that people dependent on cannabis had a significantly elevated risk of having or having had panic anxiety attacks for an extended period. The cannabis-dependent individuals also began having panic anxiety attacks on average 8.5 years earlier than those who were not dependent on cannabis. There was no difference between those who only used or abused cannabis relative to those who did not smoke at all. A causal relationship cannot be discerned from the study, but co-morbidity was common. The fact that the panic attacks began earlier among habitual smokers *may* indicate that cannabis was a causal factor in the first attack. If it was later a matter of a relapse or an actual panic anxiety syndrome is unknown.

The detailed case studies still provide the clearest illustration of cannabis-induced actual panic anxiety syndrome with or without agoraphobia (Ströhle, et al, 1998; Deas, 2000). Szuster et al. (1988) showed that cannabis can also cause relapses or a deterioration of panic-anxiety disorder. The relationship between cannabis and other anxiety syndromes has not been fully investigated.

Depersonalisation syndrome

Feelings of unreality are often part of the experience of an anxiety attack, and this holds true for cannabis-induced anxiety attacks as well. In cannabis smokers, though, these feelings of unreality may become more profound in nature, and sometimes they dominate the negative experience (Mathew et al., 1993). When these symptoms are provoked by cannabis, they are generally short-lived, as are anxiety attacks.

When feelings of unreality dominate the symptom picture and become prolonged, we usually talk of "depersonalisation syndrome". This condition appears to be closely related to the anxiety disorders, but it is considered to belong to the dissociative syndromes. From a psychodynamic point of view, they are seen as a defence

against unbearable anxiety. This condition is rarely encountered as an independent disorder in general psychiatric practice.

It is worth noting, not least in view of the rarity of the condition, that a number of cases of prolonged depersonalisation syndrome induced by cannabis smoking have been reported in the scientific literature. Several of these cases have been difficult to treat (Szymanski, 1981; Keshaven & Lishman, 1986; Moran, 1986).

Prolonged depersonalisation syndrome after cannabis smoking (as opposed to depersonalisation experiences during intoxication) is rarely mentioned in reviews and summaries of the harmful effects caused by cannabis. Consequently, it was not primarily by studying the research literature that I became aware of the connection between these conditions. A patient who was referred to my general psychiatric practice exhibited the following clinical picture:

> A district doctor referred a young man to me with "anxiety disorder following cannabis psychosis". It transpired that the young man had not had a psychosis; what he had in fact suffered from was a severe attack of anxiety the last time he had smoked marijuana – roughly six months previously. After this attack, an anxiety syndrome (panic anxiety) had persisted and progressively become more dominated by feelings of unreality. The patient had smoked cannabis fewer than ten times in all, his social situation was very stable, and he had no history of mental problems and no hereditary tendency towards mental illness. Three years later, I was able to conclude that the patient's feelings of unreality had become a constant companion to him. Sporadically occurring anxiety proper had made its appearance, and the patient's tendency towards social phobia complicated the situation. The patient was not handicapped by the symptoms, but they were a great nuisance to him and also a cause of worry. In addition to the unpleasantness of having a symptom of this kind constantly present, certain important social activities were made much more difficult. For several years, the condition resisted all attempts to treat it.

In an informative survey (Simeon et al., 2003), Daphne Simeon and her co-workers examined 117 cases of depersonalisation syndrome – which is a larger number than in earlier reports. When going through these cases, they found that the majority of the patients were suffering from a chronic condition that had persisted for 15 years on average. In no fewer than 57 of these patients, no provoking factor could be identified. In the second largest group (29 cases), stress was found to be the provoking factor, and in third place was cannabis (15 cases). A majority of the patients had a life story involving shorter or longer periods of other mental illness, mainly depression and anxiety.

11. Affective disorders: Depression, manic episodes and suicidal behaviour

Summary of Chapter 11

Studies show that there is a causal association between cannabis smoking and depression. This association is modest and presupposes an intensive and probably somewhat prolonged intake of cannabis. At least one well-done study of young people shows a moderate, but clear association.

It is unclear what this association looks like; if cannabis causes depression through a neurophysiological effect, or if the effect is "mediated" by psychosocial stress factors that are induced by cannabis.

The most common effect when people who are already depressed smoke cannabis is that the symptoms are exacerbated in the form of anxiety and dysphoria.

Many researchers dismiss self-medication. However, it is not unlikely that some people can obtain a temporary moderation of a depression with the use of cannabis with a low concentration of THC under beneficial circumstances.

Some studies of the association between very frequent cannabis smoking and *suicidal actions* indicate a high risk factor. It is unclear how much of the association is due to cannabis smoking itself. It may be most important to view cannabis smoking as the easiest distinguishable warning signal, probably an own risk factor, but above all one that is a part of an often comprehensive collection of weighty risk factors. This is particularly true of the youngest group of 14-15 year-olds.

The relationship between cannabis and *bipolar disorders* has not been as thoroughly studied as the mental disorders addressed thus far. Most indications are, however, that although the relationship is complex, the following can be established:

- Cannabis and bipolar disorder can interact in any timeline.
- Cannabis generally exacerbates and prolongs the depressive phases.
- Cannabis can induce manic episodes.
- One study shows how intensive cannabis smoking increases the risk of falling ill with a bipolar disorder within a three-year period five fold.

Affective disorders include depression proper as individual depressive episodes or as relapses into illness, chronic depression (dysthymia), manic episodes of bipolar disorder (without being a part of a manodepressive disorder) and manodepressive disorders. Suicidal behaviour includes suicidal thoughts, attempted suicide and suicide.

The reason that suicidal behaviours are discussed here is that they – like depression – are often expressions of a lowered emotional undertone. Suicidal thoughts and attempted suicide are also included on the list of criteria for depression proper and are accordingly sometimes one of many symptoms of depression. Suicidal behaviour is, however, present in several other disorders – such as psychoses and anxiety disorders – but also manifests itself without accompanying any disorder.

Depression

As previously mentioned in the summary of this chapter, there is a high degree of co-morbidity between cannabis abuse and affective disorders. For depression (*major depression*/depression proper), the following is stated in the large NESARC study: Among cannabis abusers who were dependent for a minimum of one year, 18 per cent have a depression, which is three times more than among non-abusers (Stinson et al 2006).

Up to the 2000s, researchers showed little interest in the co-morbidity of cannabis abuse and affective disorders, although the nature of the interaction was considered to be important. The question as to whether cannabis abuse could cause depression was addressed now and then.

In a well-known review article, H. Thomas (1993) looks at the question of depressive reactions. His conclusion is that it is not possible to find scientific proof that cannabis causes depressions of clinical importance. He does, however, consider that there is a large body of clinical observations showing that shorter-lived dysphoric episodes can be provoked by cannabis abuse.

Weller et al. (1989) compared abusers, users and non-users of cannabis in a group of outpatients and found that of the abusers, 55 per cent had a clinical depression according to the DSM-III criteria. They could not determine whether there was a causal connection. The cannabis abusers also exhibited a higher frequency of other problems – some of which have an established relationship with depression – such as parallel abuse of alcohol or sedatives. Moreover, the cannabis abusers had family backgrounds which featured a significantly higher level of drug abuse, alcohol abuse, criminality and suicide. The study by Rowe et al. (1995), which showed an association between marijuana smoking and depression in women, suffers from the same lack of simultaneous control for other depression-provoking factors.

Recent Studies

The three most important studies were published early in the 2000s. Bovasso (2001) conducted a study whose main objective was to shed light on two questions:

1. To what extent does cannabis abuse constitute a risk factor for the development of depressive symptoms?
2. To what extent do depressed people tend to self-medicate with cannabis?

The study was based on data initially collected in 1980 within the framework of a major psychiatric inventory of a representative selection of the adult population of a

region in the United States. A population of 1,920 persons of all ages were examined in 1995, on average 15 years after the start of the study. Two groups were studied more closely: those who had no depressive symptoms, but abused cannabis at the beginning and those who had no cannabis abuse at the beginning, but had depressive symptoms. At follow-up, it was found that among those "non-depressives" who at the start (and for an unknown period thereafter) were cannabis abusers, depressive symptoms were four times more common than among those not recorded as cannabis abusers. Further, it was found that depressive symptoms at baseline did not increase the likelihood of exhibiting cannabis abuse at follow-up. The depressive symptoms involved were mainly anhedonia (a lack of feelings of pleasure) and suicidal thoughts.

Patton et al. (2002) studied a group of school students for seven years. A total of 1,600 students from 44 different schools were monitored between the ages of 14–15 and 21–22 years. The girls ran a risk of depression that was four to five times larger with intensive (daily) use of cannabis than if they had not smoked cannabis. In line with the findings of the previous study, depressive problems during the teenage years did not give rise to increased cannabis use during early adulthood.

In one of their many studies of the children/adolescents in one of New Zealand's birth cohorts in Christchurch, Fergusson and his colleagues studied 1,265 children/adolescents/young adults from the age of 14 to 21 (1. Fergusson and Horwood 1997, 2. Fergusson, Horwood and Swain-Campbell 2002). They monitored cannabis consumption, other drugs and a number of psychosocial outcomes, including depression, suicidal acts, transitions to severe substance abuse, criminality, etc. Since the children and their growth environment in a birth cohort were studied from a tender age, the researchers also had access to a large amount of data on potentially co-varying factors. In this case, a very sophisticated study design was also used. Two versions of the study by Fergusson et al were done, one in 1997 and one in 2002. In the latter, a longer follow-up period could be used, as well as more relevant definitions of intensive cannabis abuse, etc. With regard to depression (generally major depression) in the three age groups (14-15, 17-18, 20-21 years), 27-30 per cent of those who smoked cannabis at least once a week showed signs of depression. After applying controls for co-variant factors, it was found that the moderate average increase in risk, expressed as risk relative to high consumption of cannabis compared with no consumption, was 1.7.

Is there a causal association between cannabis abuse and depression?

The three studies I presented above and a few others were summarily assessed in reviews: In a large review done a few years ago, Theresa Moore, Stanley Zammit and colleagues (2006) reviewed seven studies of cannabis-induced psychosis (see the chapter on schizophrenia) and 15 studies on the relationship between cannabis and depression/act of suicide. The group of depression studies was so heterogeneous in a number of respects, however, that they did not consider it to be meaningful to conduct a meta-analysis. Criticism was directed at weaknesses in all of the depression

studies. Some had not corrected for co-variant factors, half had not corrected for alcohol and other drugs, and so on. None of the studies had controlled in a reasonable manner that recorded depressive symptoms were not expressions of toxic reactions due to cannabis intoxication (intoxication often, particular at higher doses, includes *dysphoria* and *anxiety*, and *dejection/depressiveness* is not an uncommon withdrawal symptom). The group deemed that the depression studies were weaker than the psychosis studies.

In a review, Louisa Degenhardt, Wayne Hall and Michael Lynskey (2003) found that only intensive cannabis abuse can provide an elevated risk of depression later in life, although the increase in risk is not very large. They point out that there is a lack of cohort studies that include adults, while there are several that shed light on the adolescent years. They also mention the need for genetic research in the area.

Degenhardt et al (2003) looked at other conceivable ways that cannabis may provoke depressions. From the studies the group reviewed, particularly Ferguson et al, and from other sources, a view came forth that it is not primarily through neurophysiological influence that cannabis causes depressions. Several of the studies refute the self-medication hypothesis. Degenhart et al were struck by how the psychosocial problems caused by cannabis abuse – poor results in school, unemployment, criminality – in many regards coincide with the factors that can usually underlie psychiatric problems such as depression and acts of suicide. Viewed from this approach, cannabis influence can be said to be mediated by psychosocial problems that later cause depressive symptoms. Future studies will have to show whether or not this is the dominant pathway, at least for the young.

In terms of the effect that cannabis has on an existing depression, most observations and studies indicate that, if it has any effect, it is that the depressed person is filled with anxiety and becomes more dysphoric (Degenhardt et al, 2003; Mikkel Arendt et al, 2007). One study found "no effect at all" in habitual smokers, but a deterioration through greater dysphoria in beginners (Degenhardt et al 2003).

In summary:

- Studies show that there is a causal association between cannabis smoking and depression. This association is modest and presupposes an intensive and probably somewhat prolonged intake of cannabis.
- At least one well-done study of young people shows a moderate, but clear association.
- It is unclear what this association looks like – if cannabis causes depression through a neurophysiological effect, or if the effect is "mediated" by psychosocial stress factors that are induced by cannabis.
- The most common effect when people who are already depressed smoke cannabis is that the symptoms are exacerbated in the form of anxiety and dysphoria.

- Many researchers dismiss the self-medication theory. However, it is not unlikely that some people can obtain a temporary moderation of a depression with the use of cannabis with a low concentration of THC under beneficial circumstances (Ashton et al, 2005).

Cannabis and acts of suicide

Acts of suicide are brought up in this context because depression (major depression) is the psychiatric disorder that results in the highest risk of suicide (20 per cent), and probably also the other suicidal behaviours (suicidal thoughts and attempted suicide). Other disorders and conditions are also associated with high suicide mortality. Schizophrenia also results in a 20 per cent risk of suicide.

The frequency of suicide among drug addicts – taken as a group, without consideration of contributing factors – is believed to be 20 times higher than in the average population. Approximately 15 per cent of all alcoholics (alcohol dependence) commit suicide, often late in the course of the disease. There are some conditions that are clearly of central importance to the risk of acts of suicide in those dependent on cannabis. Among these are co-morbidity, especially with schizophrenia or severe depression, and poly-drug abuse, particularly alcohol on a dependent level. In an assessment of the risk, it is also two main weighty provoking factors that we must consider: *losses* of people (or animals) and *violations* in a broad sense. Divorce can be one example of the former and definitive unemployment an example of the latter type (Cullberg J. 2000).

The most important relationship between *attempted suicide* and consummated suicide is that a high proportion of suicide attempts, 10-20 per cent, are later followed by consummated suicide.

Studies of the relationship between cannabis abuse and acts of suicide

Andréasson and Allebeck (1990) studied large-scale cannabis consumers in a group of 45,000 Swedish military conscripts. They found excessive mortality in the cannabis group, but after controls were made for other factors, this excessive mortality could not be linked to cannabis as a sole cause of death (violent death was the dominant cause of death; 34 per cent had died from suicide or suspected suicide). The authors point out that the association between cannabis and other illegal drugs (for which there is a documented increased mortality, not least from suicide) indirectly affects mortality. In a similar fashion, cannabis indirectly increases the risk of suicide as a result of its ability to precipitate, exacerbate and cause psychosis and depression.

There is reason to remind the reader of one of the findings from the study by Bovasso et al. (2001) mentioned above. Of the depression variables investigated in that study, two were reported by the subjects particularly often: anhedonia (a lack of feelings of pleasure) and suicidal thoughts.

Fergusson et al (2002) also recorded suicidal thoughts and suicide attempts. They found strong associations in the younger ages (14-15 years), while the associa-

tion between smoking "at least once a week" and thoughts of suicide and suicide attempts largely vanished in the oldest age group (20-21 years).

In the young group, the risk of suicidal thoughts was 7.3 times larger for cannabis smokers than non-smokers. There was a 13.1 times greater risk of attempted suicide among high consumers of cannabis than the non-smokers. With regard to these suicidal acts, there is even more doubt about a direct neurophysiological effect than with regard to depression. The effect of cannabis is mediated in some way, but it is unclear how.

Beautrais et al (1999) studied 302 patients admitted to hospital due to a serious suicide attempt. A randomly selected control group was subjected to the same battery of questions regarding background factors, childhood conditions, current mental illness and cannabis habits as those who attempted suicide. The results showed that the association between cannabis abuse/dependence and attempted suicide was largely due to

a. the fact that those who developed substance abuse (which was ten times more common in the study group) had grown up under sociodemographically disadvantaged conditions and had many childhood experiences that, independent of cannabis abuse, entail a higher risk of attempted suicide.

b. The cannabis abusers had a co-morbidity with several mental disorders and other substance abuse, which by their own effect result in an elevated risk of suicidal behaviours.

The authors summarise with the conclusion that, despite that described above, it is entirely possible that an increase in risk remains directly connected to the cannabis abuse.

Suicide committed by jumping from a height

In an unpublished study of 53 suicides likely to have been committed by means of jumping from a height, Fugelstad, Gerhardsson de Verdier and Rajs (1995) found that a disproportionately large share (11 per cent) of the jumps had occurred under the influence of cannabis. By taking into account the proportion of abusers in the age group concerned (20–34 years), the researchers were able to calculate the increased risk of committing suicide by jumping from a height. A cannabis smoker is 18.7 times more likely than a non-smoker to take his or her life by jumping from a height. It is unclear whether this is actual suicide or if it is a combination of death wishes and delirium induced by smoking cannabis. This study can in continuation be seen as a very interesting clinical observation. The study initiated will be extended.

Bipolar disorder

From the aforementioned, major U.S. study (NESARC), Stinson indicates the *prevalence* of co-morbidity such that 26 per cent of those who have been cannabis dependent for the past 12 months have a bipolar disorder (Stinson et al 2006).

Does cannabis provoke manic episodes?

Within the framework of the Dutch NEMESIS project (3,854 people), van Laar and her colleagues studied how much greater the risk was for cannabis smokers to develop a bipolar disorder over a three-year period compared with those who did not smoke cannabis. They found that the risk of the initial onset of a bipolar disorder was five times larger among cannabis smokers (Margriet van Laar et al 2007).

Interaction between cannabis smoking and bipolar disorder

A U.S. research group wanted to study the interaction between cannabis smoking and bipolar disorder.

They monitored 144 consecutive cases of those treated for bipolar disorder for the first time. They were divided up into three groups, one without co-morbidity with cannabis abuse and two groups with co-morbidity. In one group, cannabis smoking had preceded the debut of the bipolar disorder by at least one year, and in the other group, the disorder became manifest prior to the cannabis abuse. The abuse ended in connection with hospital stays as well as a period after release. Accordingly, there were repeated periods during which the co-morbidity was interrupted. It came forth that the relationships are complex and are complicated by a high proportion also abusing alcohol. Some of the conclusions were the following:

- In the "cannabis first" group, there was reason to assume that cannabis had provoked/caused the onset of the disorder. On average, this group was five years older at onset than the patients in the other groups. They also appeared to have low degrees of vulnerability.
- Cannabis is abused in both depressive and manic phases.
- The bipolar disorder was generally exacerbated during relapses into cannabis abuse.
- In the co-morbidity groups, there was a direct correlation between the two conditions so that the longer the periods of abuse were, the longer the depressive phases became. No support was found for the idea (proposed by Ashton et al 2005 among others) that cannabis could mitigate the symptoms of bipolar disorder.

12. Amotivational syndrome

Summary of Chapter 12

"Amotivational syndrome" is a well-established term which aptly describes the particular personality traits of many chronic cannabis abusers. Many clinicians and some researchers have described this syndrome as a specific, yet complex, illness provoked by cannabis. Some have been of the opinion that these traits agree with a depressive syndrome best, and others have pointed out the similarities with the "negative" schizophrenic symptoms in particular.

Both depressive elements and psychosis symptoms agree with what we know about the effect mechanisms of THC, but the syndrome's core symptoms are primarily expressions of chronic cannabis intoxication. The continual impact on cognitive functions in particular leads to a mental state characterised by varying degrees of apathy, loss of effectiveness and reduced ability to carry out complex, long-term plans, to deal with frustration, to concentrate for any length of time, to follow routines or to deal successfully with new situations.

In 1968, Smith introduced the term "amotivational syndrome", and in the same year McGlothin and West described the particular personality traits of cannabis smokers under the heading of *amotivational personality characteristics*. These two notions referred to the same condition, which the researchers had observed mainly in North American young people (Cohen, 1982). Although it has been difficult to find scientific evidence for the existence of such a syndrome induced by cannabis, the ubiquity of the term "amotivational syndrome" is remarkable. It is clear that it has struck a chord as an apt description of particular personality traits frequently observed in chronic cannabis smokers.

Amotivational syndrome accordingly refers to a cannabis-induced mental state characterised by "apathy, loss of effectiveness, and reduced ability to carry out complex, long-term plans, deal with frustration, concentrate for any length of time, follow routines, or deal successfully with new situations" (Cohen, 1982).

The descriptions of the condition agree in part with older observations of large-scale consumers of cannabis preparations in certain developing countries. On the other hand, it is precisely studies from developing countries (and Greece) that have shown the absence of amotivational syndrome: Comitas (1976) in Jamaica, Carter and Doughty (1976) in Costa Rica, and Boulougouris, Liakos and Stefanis (1976) in Greece.

The clinical reports which support the existence of amotivational syndrome appear primarily to build on observations of young individuals in Western industrialised countries (Cohen in *Marijuana and Youth*, 1982; Tunving, 1987). Newcomb and Bentler

(1988) also claimed to have found some evidence supporting the existence of amotivational syndrome in their longitudinal study of a large group of young people.

Cohen (1982) maintains – drawing part of the support for his claim from a study by Soueif (1976) – that chronic cannabis abuse does not produce these motivation-inhibiting effects in illiterate abusers who are manual labourers and live in a rural, less intellectually demanding cultures. Instead, those affected by the condition are not least young people living in the complex, urban environments of the modern Western world, where considerable demands are made on people with regard to intellectual performance, a readiness to adapt rapidly to change and a willingness to re-learn quickly.

What Soueif (1976) discovered was that the differences (in terms of scores on tests of cognitive and psychomotor functions) observed in a large study between a group of chronic cannabis smokers and a group of non-smokers more or less disappeared when the subgroup of "illiterate rural people" within the broader group of cannabis smokers was compared with the non-smokers. On the other hand, the differences were amplified when the subgroup of "literate urban people" was compared with the non-smokers.

One circumstance worth drawing attention to is the fact that in many studies, including the one just mentioned, poor levels of motivation are equated with lower scores on tests which primarily measure cognitive and psychomotor ability. While the effect exerted by chronic cannabis smoking on cognitive functions undoubtedly affects mental processes which may contribute to "amotivation", the processes we are dealing with here are probably not exclusively cognitive in nature. According to Musty and Kaback (1995), this deterioration in motivation may perhaps be due to elements of depression and, as per Hélène Verdoux et al (2002), negative psychotic symptoms.

In conclusion, then, it can be said that the term "amotivational syndrome" seems to be a strikingly apt description of the particular psychosocial personality traits of a not insignificant proportion of chronic cannabis abusers, especially among young cannabis smokers in Western industrialised countries. These traits, which seem to be elusive to scientific documentation, can be confused with – or reinforce – other states or conditions, including periods of regression during the teenage years which are appropriate to that phase from the perspective of developmental psychology, as well as depression, chronic tranquil schizophrenic psychosis and certain personality disorders.

Consequently, these psychosocial personality traits are in all probability a manifestation of certain effects of chronic cannabis intoxication and mild forms of co-morbidity, especially with depression and psychotic symptoms.

The markedness of these personality traits would seem to be dependent on the "cerebral reserve" at the individual's disposal, as well as on the social support at the individual's disposal. The individual and those in his or her surroundings more easily notice the functional deterioration the greater the demands become that the individual is faced with. It seems reasonable to say that our modern high-tech society, with the many demands it places on individuals and its rapid pace of change, is a social environment which is more or less incompatible with chronic cannabis intoxication.

13. Cannabis and violence

Summary of Chapter 13

Generally speaking, the effect of cannabis is to soothe and to calm rather than to stimulate aggression. Research into the relationship between the effects of cannabis and acts of violence, however, has produced ambiguous findings.

This chapter presents a few case studies showing an association between cannabis and serious violence (murder, manslaughter and aggravated battery). These studies, along with clinical observations, underline the importance of studying the co-morbidity of cannabis abuse and personality disorders, and that of cannabis abuse and psychosis as well.

The studies presented in this chapter once again highlight the need to study the interaction between cannabis and alcohol.

Niveau and Dang join many others in pointing out that the stronger preparations increase the risks. Stronger preparations seem particularly more likely to cause toxic psychosis or delirium.

Most researchers agree that the effect of cannabis is normally (i.e. in the case of the average abuser) to calm and to induce passivity rather than to stimulate aggressiveness. However, owing to the dramatic nature of the effects produced by cannabis on the mind and to clinical observations of violent acts, the question of whether cannabis might be associated with aggressiveness and acts of violence has been raised repeatedly. A large number of commissions and conferences have focused on this issue (Abel, 1977; Rosenberg et al., 1984). In all cases, the conclusion reached has been a similar exonerative verdict of "not guilty".

Abel (1977) does, however, point out that a weakness shared by all these reports is that in general, they have not looked at the question of the effect produced by cannabis on individuals who are especially vulnerable in this respect – above all, mentally fragile people with low levels of impulse control and people with psychoses, borderline psychotic conditions, profound personality disorders and brain damage.

There seems to be no study that shows, in a methodologically satisfactory manner, that cannabis is in any way linked with violence. The explanation may have something to do with Abel's aforementioned point of view. If you add in the fact that the primary objective of most studies is to identify pure effects of cannabis, the findings are easier to understand. In stable, mentally healthy people, the calming effects usually predominate. As can be seen from the case studies referred to below, it appears to be precisely the *combination* with a mental disorder that may sometimes lead to unfortunate consequences.

When it comes to alcohol and illegal drugs other than cannabis, we increasingly speak in terms of "dual diagnosis" or "co-morbidity", taking an interest in the interaction between two or more conditions. It seems to be time that we studied not only the interaction between cannabis and schizophrenia, depression and anxiety illnesses, but also systematically study the connection between cannabis and various personality disorders.

Moreover, the studies mentioned below remind us once again how important it is to study the interaction between alcohol and cannabis in these contexts as well.

A few case studies in the field of cannabis and violence

Spunt et al. (1994) conducted a study which shows that in certain cases of aggravated violent crime there is probably a connection with cannabis intoxication. They interviewed 268 people sent to prison for murders committed in New York State during 1984. Of these inmates, 73 had been under the influence of cannabis when they committed murder; and of these, 18 were of the opinion that there was a link between the murder and the effects of cannabis. The persons interviewed were also asked *how* marijuana smoking affected them. Four of them gave answers along the lines of "it made me aggressive, violent", one answered "when I am high I just lose control …", and another said "I don't think I would have done anything if I hadn't been under the influence". Four interviewees gave answers of the type "it lowered my inhibitions", and two replied along the lines of "it made me feel paranoid".

Of the 18 murderers who had been under the influence of cannabis, 15 were also under the influence of alcohol or an illegal drug other than marijuana. Nine of these said that they thought the combination of cannabis with alcohol – or of cannabis with another drug – was an important factor in their committing the crime. One of the three who were under the influence of only cannabis and alcohol explained the effect in the following manner: "One alone you can handle – but two together confuse your mind." Another of them said: "The alcohol took away my inhibitions and the pot made me crazy." And the third of them observed: "The combined effect made me lose self-control."

Niveau and Dang (2003) have accounted for 12 cases of aggravated violent crime, all committed in Geneva in the period 1996–2000. Initially, there was a much larger study group, but those with poly-drug abuse were excluded. When committing the crime, the individuals in question were under the influence of cannabis only. Of the 12 subjects, five had a previously known personality disorder and three had other psychiatric disorders.

At the time of the crime, all 12 were suffering from severe negative effects caused by cannabis consumption: four of them experienced acute psychotic conditions and one suffered a relapse into or an exacerbation of chronic paranoid psychosis. A further three of them experienced negative reactions such as intensive anxiety (the description is somewhat unclear on this point) and three were affected by delirium. One patient had an "affective disorder".

The report is densely written and my space here is limited. What I wish to emphasise most of all is what appears to be, at least in some cases, an unfortunate combination of vulnerability (mainly to psychotic disorders), cannabis use and a current stressful situation whose effect has been to provoke psychosis, delirium and attacks of rage, all with a strong element of aggression.

Arsenault et al studied 961 young adults (94 per cent of the birth cohort of Dunedin) with regard to mental illnesses, abuse and co-morbidity relative to the group's acts of violence in the past year (20th year of life). The cannabis abusers had a 3.8 times greater risk than the non-smokers of committing violent acts during the year of observation. There was a significant co-morbidity with *conduct disorder* (the precursor of antisocial personality disorder), which was a partial explanation of the association (Arsenault et al 2000).

In other words, here we see two shifts in perspective as regards the dangerousness of cannabis. There is growing interest in dual diagnoses involving cannabis abuse as one of the disorders, and there is also growing interest in the interaction between alcohol and cannabis. (In addition to the discussion presented in this chapter, the reader should also refer to Chapter 16 on cannabis and driving.)

Part 3. Some psychological and psychosocial harmful effects

14. Harmful effects of smoking cannabis on capacity of thinking, memory and sense of coherence (cognitive functions)

Summary of Chapter 14

A deterioration of cognitive functions is the most important harmful effect of cannabis.

The acute psychotoxic effects caused by cannabis smoking on cognitive functions (memory functions, attention, concentration, analysis and planning ability) arise after a single intoxication. Measurable effects remain from three to 24 hours, depending on the size of the dose and how it was taken.

In the case of repeated consumption, one or more times a day, the functional impairments will persist (even though the individual learns how to hide certain functional shortcomings) and the entire personality will eventually become marked by above all cognitive difficulties, and also by the social strategies used by the individual to compensate for the deficiencies.

The manifestations of the chronic effects include the following:

- decreased ability to carry out complex thought operations
- reduced ability to concentrate
- decreased capacity for maintained attention
- reduced ability to process information
- impairment of short-term memory
- reduced intellectual flexibility
- reduced ability to learn from experience
- lowered ability to carry out long-term strategic planning.

The abuse also causes difficulties expressing oneself verbally in new, unfamiliar situations where old modes of thought and old knowledge are inadequate.

Chronic abuse also leads to a measurable deterioration in the individuals' "sense of coherence" (i.e. their perception and understanding of their environment). However, this effect fades a number of weeks after abuse is discontinued – or sooner if treatment is given.

Systematic clinical observations of cannabis abusers yield a picture of a personality characterised by rigidity, inflexibility and memory problems – and consequently problems in dealing with change. Cannabis abusers are not seldom lonely and isolated people..

Studies of chronic abusers show that certain functional defects (typically subtle ones) persist for several years after the individual has discontinued his or her abuse. The functions affected relate mainly to memory and attention.

We are dedicating an entire chapter to cognitive impairment because it is such a central manifestation of cannabis use, cannabis abuse and cannabis dependence.

With only a single normal intoxication, the cannabis intoxication causes a transient deterioration of *cognitive functions*. This primarily is related to memory ability, temporal perception (including the ability to assess lengths of time), attention difficulties and concentration difficulties. At high doses or repeated intoxication, more complex functions are affected such as learning ability, executive functions and both flexibility and endurance with regard to attention. Cannabis intoxication also causes a deterioration of *psychomotor functions* such as coordination, balance and reaction speed.

The acute deterioration of these functions and its importance for (above all) driving will be discussed in Chapter 16. The cognitive disturbances might possibly be at the core of the mental weaknesses which provoke psychosis and other mental symptoms. Chapter 17 accounts for late mental effects on children whose mothers have smoked cannabis during pregnancy. The symptoms exhibited by these children are similar in many respects to some of the cognitive disturbances which arise in cannabis-smoking young people and adults.

This chapter looks at the question of how chronic cannabis abuse affects mental functions – i.e. what happens to human cognitive and psychomotor functions if the brain is exposed to constant and prolonged cannabis intoxication. It is reasonable to assume that repeated poisoning, month after month and year after year, will produce some form of exacerbated negative effects, and it is also reasonable to assume that those effects do not consist solely of the repetition of the effect of occasional poisoning.

A particularly interesting aspect of this relates to the effects it has on personality: on the experience of self, on the individuals' perception of their environment, on their ability to function at the psychological and social levels, on their ability to develop personal maturity, and so on.

Studies and observations can be classified as laid out below, according to the types of harmful effects to which they refer:

a. Permanent brain damage following cannabis smoking (covered along side the main theme in the section, since it concerns structural harms with an unclear relationship to cognitive damages).

b. Damage to cognitive mental functions while under chronic cannabis influence

c. Effects on complex mental functions such as the sense of coherence and the ability to process new impressions and one's own memories

a) Permanent brain damage following cannabis smoking

The term "brain damage" as used here refers to permanent damage which can be demonstrated radiologically while the individual is alive or by means of microscopic investigation of the brain of a deceased abuser.

There are many clinical and anecdotal reports describing prolonged impairment of mental functions in chronic abusers of cannabis, not least from developing countries. These observations are supported by early scientific studies (e.g. Chopra, 1976; Soueif, 1976). Even though these studies have severe limitations due to unsatisfactory scientific design, they contributed strongly to placing the discussion of permanent brain damage on the scientific agenda at an early stage.

Campbell et al. (1971) caused something of a sensation by publishing a study where they showed the existence of cerebral atrophy (withering of the brain) using air encephalography on ten chronic cannabis abusers while thirteen controls of the same age returned normal results. This study was severely criticised on several counts from a methodological point of view and proved to be unrepeatable by other researchers. Several other studies have been done using computer tomography (body-section radiography), in which cerebral atrophy could not be detected in chronic cannabis abusers (Hannerz & Hindmarch, 1983).

Yücel, N.Solowij, et al (2008) conducted a cross-sectional study of 15 carefully chosen cannabis abusers who had smoked at least five cigarettes a day during at least ten years of substance abuse (They had no background of other drugs, alcohol or mental problems, but an average of 20 years of cannabis abuse.) and 16 matching control subjects.

The study was primarily directed at the difference between the groups with regard to volume differences of the hippocampus and amygdala (structures in the brain's temporal lobes) as shown by magnetic resonance imaging (MRI). Some tests were also done to assess possible psychotic symptoms. Because urine tests indicated the current influence of cannabis, these later results of the study were difficult to assess. The structural study indicated significant bilateral reductions of the volume of the amygdala and hippocampal complexes. The individual decrease of the left hippocampus showed a direct relationship to the total cannabis dose and the extent of mild psychosis symptoms of the individual abuser.

The temporal lobes, of which the amygdala and hippocampal complexes are a part, are one of the most common areas that usually exhibit a reduction in volume in schizophrenic patients through common neurodegeneration (B. R. Rund 2009). This may possibly be another piece of the puzzle in explaining the relationship of cannabis to schizophreniform psychoses.

In a five-year prospective longitudinal study, Monica Reis and her colleagues compared first-time onset in schizophrenic patients divided into cannabis smokers (19) and non-cannabis smokers (32). The cohort also included 31 healthy control subjects. The brain's volume was measured using MRI at onset and five years later. The cannabis-smoker group showed a significantly larger decrease in brain volume compared with the other two groups (Reis M. et al 2008).

b) Damage to cognitive mental functions while under chronic cannabis influence

Scientific studies

In 1986, Wert and Raulin made two wide-ranging reviews of all studies that had been carried out in this field up to that point. They found that neither neurological nor neuropsychological studies had shown unambiguously that chronic abusers suffered from structural or functional damage caused by their chronic abuse (Wert & Raulin, 1986a; 1986b).

However, Wert and Raulin do discuss the possibility that the "differential impairment" (in groups equally exposed to cannabis abuse and having experienced similar conditions in other respects, some subjects exhibited damage while others did not) found in many studies might not be a consequence of faulty study design, but rather a manifestation of varying vulnerability in different individuals. The authors write:

> It might well be that some individuals are predisposed to cerebral impairment as the result of cannabis use, either because of structural or biochemical characteristics which accentuate the possible damaging effects of the drug, or because they have little of the cerebral reserve that most of us call on when we experience mild cerebral damage. That functional reserve can mask very real cerebral damage.

This kind of interaction between stress/damage on the one hand and vulnerability on the other is now an accepted model for explaining both how many illnesses arise and why some people do not fall ill although they are exposed to a stress factor. Generally, however, we know very little about these vulnerability factors in each individual case. This line of thinking is obviously valid for many of the harmful effects dealt with in this report.

With regard to what were, after all, the dominant findings, i.e. no proven damage as a result of prolonged cannabis use, it could not be excluded that the testing methods may not have been sensitive enough. However, Wert and Raulin's answer to that objection was that it was indeed possible, using the same testing methods, to detect brain damage in alcoholics.

Subsequent studies have proved them right: the damage caused by cannabis smoking is not only of a more subtle type than had previously been expected, but it is also different in nature.

A couple of studies returned to earlier study groups where the original study had not been able to prove the existence of any cognitive damage. Renewed testing, which made use of more sophisticated methods, found clear differences between abusers and non-users, especially with regard to the ability to sustain attention and the ability to remember something just learned (short-term memory) (Page et al., 1988).

By using more specific testing methods and applying a more rigorous methodology, a number of studies have shown that prolonged use of cannabis causes damage in the cognitive sphere, particularly with regard to specific aspects of memory and attention as well as the organisation and integration of complex information. In order to exclude the effects of acute intoxication, the tests were carried out after at least 24 hours' abstinence from cannabis smoking. (We now know that this is too little time.) In general, there was found to be an association between the duration of the cannabis-smoking habit and the degree of functional impairment measured: the longer the period of abuse, the worse the test score.

Block et al. (1990) showed that intensive, prolonged cannabis smoking is detrimental above all to the ability to express oneself verbally and to solve mathematical problems. Solowij (1995a; 1995b; 1999) has shown that prolonged cannabis use leads to impaired ability to focus attention and to screen out irrelevant information. Schwartz et al. (1989) showed, in a study which is discussed in greater detail in the chapter on teenage development (Chapter 15), that cannabis smoking resulted in a significant impairment of short-term memory which persisted for at least six weeks after the individual stopped smoking. Leavitt et al. have presented their findings only at scientific conferences (reports which I have not had the opportunity to read), but their results are reported in reasonable detail by Hall et al. (1994, p. 138) as well as by Lundqvist (1995, pp. 46–47). 46–47), who concurs with the opinion of Leavitt et al. that they and other researchers have shown that long-term use of cannabis entails, among other effects, the following:

- impaired ability to carry out complex thought operations and impaired ability to screen out distracting impressions
- reduced ability to process information
- no effect on long-term memory, but impaired short-term memory, particularly with regard to information which is of a kind unfamiliar to the individual or which is complex in nature
- difficulty in carrying out tasks which require intellectual flexibility, long-term strategic planning and the ability to learn from experience
- no effect on the ability to deal with the routine, familiar demands of everyday life, but problems when faced with the task of expressing oneself verbally in a new, unfamiliar situation or in a situation where old ways of thinking and old knowledge are inadequate.

Does cognitive damage remain after detoxification?

1) Is there a *residual effect*?

This expression refers to a measurable effect (such as with a relevant test) that remains even though there is no significant level of THC or any active metabolite left in the person's blood (occasionally referred to as a *carry-over effect*) (Pope et al

2001). As outlined in Chapter 2, we do not know where this limit goes, especially with repeated, high-level cannabis consumption. Storage in fatty tissue is one factor, among others, that complicates matters. There is, however, reason to believe that some form of residual effect does exist (Pope H.G. et al 2001). It may possibly be in relation to the amount of cannabis previously consumed (N. Solowij 1999). This effect is also related to the sensitivity of the test and the level of difficulty of the task.

A few examples: Leirer's evidence of an effect on pilots 24 hours after the intake of 20 mg THC may reasonably be related to the fact that landing an aircraft places great demands on cognitive ability (see Chapter 16). At this time, with this dose, there has been no measurable amount of THC in the blood for several hours.
The young people in Schwartz's study (see Chapter 15) were long-term users of high doses. The boys had memory disturbances for at least six weeks, or possibly longer, after their abuse ended.

2) Can the cognitive damage become permanent?
To my knowledge, there is only one study that definitely passed the longest time that it can take for THC to leave the body in testing. This is Solowij's study of the ability of long-term addicts – on average four years after the end of abuse – to manage a sensitive test of "the ability to focus attention and filter out irrelevant information". The test subjects had a very moderate, but permanent functional impairment.

A couple of research groups have shown that cannabis smoking during pregnancy can cause cognitive damage to the child that has proven to be permanent in follow-ups that were more than a decade long (see Chapter 17).

It seems that the growing foetus and the growing person in the early teenage years (as we will show in the chapter on teenagers) are the most vulnerable to this type of effect.

Clinical observations related to research findings

In his PhD thesis, Thomas Lundqvist (1995) looked at the cognitive damage arising in connection with prolonged cannabis smoking. He presented a model for categorising the cognitive functions at issue, a model which he had been using for a number of years to organise clinical observations of cognitive functions in 400 long-term cannabis abusers who had sought care at an outpatient clinic. Together, these clinical observations provide a very informative illustration of and supplement to the scientific studies referred to above. In a small-scale study (which will be accounted for in the next section), Lundqvist sheds more light on the disturbances to chronic abusers' experience of the surrounding world.

Lundqvist's clinical observations regarding cognitive disturbances, when placed in relation to scientific studies, lead both to a treatment model for cannabis abusers and to a number of interesting hypotheses and figures of thought concerning the direct effects of cannabis on the various structures and functions of the brain. However, those parts of the thesis fall outside the scope of this report.

It is worth noting in its own right that over 1,000 cannabis abusers have sought help at the treatment centre where Lundqvist works. Even though the functions necessary to assess their need to stop abusing will have deteriorated as a result of their abuse, many cannabis abusers still wish to make an attempt to change their life situation. This is a reflection of the fact that cannabis abusers suffer from their dependence and their functional impairments.

Lundqvist divides the cognitive functions which are impaired when the individual is under the influence of cannabis into the following categories:

Verbal ability
Having a vocabulary that corresponds to one's age, finding the words for what one wants to say, understanding others and having the ability for abstract thought.

Logical-analytical ability
Ability to analyse and draw logical conclusions, ability to understand causal connections and ability to judge oneself in a critical, logical manner.

Psychomotility
Ability to maintain attention and to vary the degree and focus of attention. Ability to understand other points of view and to change one's own point of view. Some degree of general flexibility with regard to different ways of looking at and interpreting societal phenomena.

Memory

- Short-term memory/working memory: Ability to remember what has just happened or been communicated, which is a prerequisite not only for the integration of what has just been communicated, but also for the integration and organisation of a whole range of cognitive processes, as well as a precondition for a reasonably adequate temporal perception.
- Long-term memory: This consists of both "episodic memory", which makes it possible to remember events and their temporal context, and "semantic memory", which has more to do with what we call "knowledge", e.g. different facts and the inter-relationships between different phenomena.

Analytical and synthetic ability
Based on the ability to combine the other functions. Makes it possible to synthesise, sort out and organise mental material.

Psychospatial ability
Makes it possible to orient oneself, other people and various phenomena in time and space, which is a precondition for temporal organisation as well as one of the prerequisites for social orientation.

Gestalt memory (holistic memory)
Enables us to understand and form patterns – not only to understand that there is a connection, but also to understand its nature and structure. For example, enables us to make and maintain the connection between a person, a name and a social role.

All of these functions were disturbed, to a greater or lesser degree, in the cannabis abusers who sought help at the treatment centre. Systematic interviews were carried out with ten former chronic cannabis abusers, between two and 48 months after they had discontinued their abuse, about the changes they felt they had gone through. All of them said that their way of thinking and the way they perceived the world around them had changed after they had stopped smoking. Above all, they felt that their verbal ability, their logical-analytical ability and their psychomotility had improved.

c) The effect of cannabis abuse on the abusers' understanding of the surrounding world as expressed in their "sense of coherence"

Antonovsky (1987) has developed *sense of coherence* (SOC) into a clinical and scientific notion. He found that people who had been better than others at dealing with demanding, traumatic experiences in their lives had a more developed sense of coherence. SOC can be seen as constituted of three components:

- *comprehensibility* – being able to understand the situation in which one finds oneself and the traumas one is exposed to;
- *manageability* – being able to handle a situation or act upon it, or being certain that somebody whom one trusts will act in one's interests;
- and *meaningfulness* – in the sense that the strains to which one is subjected are in some way meaningful.

Antonovsky has developed a test which measures a person's degree of SOC. Lundqvist (1995c) tested 15 cannabis abusers on two occasions – when they were admitted and six weeks later, i.e. after six weeks of both abstinence and treatment. On admission, the average test score was 118.2; six weeks later it had risen to 141.9. This represents a statistically significant improvement, both for SOC as a whole and for each of its three components. Following treatment, the former abusers obtained scores close to those achieved by the control group consisting of non-abusers with university degrees, whose average score was 153. (According to Antonovsky, in a country such as Sweden, scores between 143 and 153 are to be seen as reflecting a good level of adaptation in these respects.) These improved levels were recorded although it can reasonably be assumed that the recently detoxified former abusers

were not yet in a state of full mental balance – a circumstance which has been shown by experience to result in lower SOC scores. It was also found that cannabis abusers, who had undergone a period of abstinence but had not received any treatment, obtained a significantly worse score than the group that had received treatment.

Even though this is a single study, and taking into account that it is not entirely clear exactly what is measured by the test, this research into the understanding of the surrounding world supports the position that prolonged cannabis abuse weakens the individual's ability to maintain a functional relationship with the world around him or her.

What is the importance of the cognitive damage to the individual?

Even though the mechanisms involved are unknown to us, it seems reasonable to assume that the impairments in cognitive functionality play a significant part in several of the harmful psychiatric effects described in the opening chapters of this report.

In Chapter 15, "Cannabis smoking in teenagers", I discuss the impact on the individual of prolonged cannabis smoking during the teenage years, especially as regards its effects on learning and schooling and on psychosocial development.

The impact of this cognitive damage on the individual's ability to operate complex machinery, above all vehicles in traffic, is the subject of Chapter 16, "Cannabis and driving".

Obviously, a reduction in memory capacity affects the learning ability of adults in a broad sense. There is good reason to recall Wert and Raulin's thoughts with regard to "differential impairment", which we looked at in the previous section. The harmful effects produced are doubtless dependent in large part on the extent to which the individual is able to compensate mentally and socially.

Lundqvist (1995b) found, in his clinical assessment of the 400 chronic cannabis abusers, that most of them displayed more or less pronounced weaknesses in all seven cognitive categories (and certain emotional disturbances also seem to be part of the picture).

Moreover, Lundqvist claimed that he could distinguish a typical personality profile characteristic of cannabis-smoking clients. According to this profile, abusers typically:

- have difficulty in finding the words to express what they really mean
- have a limited ability to be amused by or enjoy literature, film, theatre and the like
- have a feeling of boredom and emptiness in everyday life, along with feelings of loneliness and of not being understood
- externalise problems and are unable to take criticism
- are convinced that they are functioning adequately
- are unable to examine their own behaviour self-critically

- feel that they have low capacity and are unsuccessful
- are unable to carry on a dialogue
- experience difficulty in concentrating and paying attention
- have rigid (fixed) opinions and answers to questions
- make statements such as "I'm different, other people don't understand me, I don't belong to society"
- do not plan their day
- think they are active because they have many on-going projects – which they seldom see through to completion
- have no daily or weekly routines.

Lundqvist bases what he has to say on his extensive clinical experience of how a new identity develops in the chronic abuser. Even if one may not wish to be quite so categorical, what emerges is clearly a picture of rather special personality traits: rigidity, inflexibility, difficulty in remembering and thus generally in dealing with changes in the surrounding world, loneliness and a tendency towards isolation. These personality traits are doubtless dependent both on the size of the dose and on the duration of abuse; but the cognitive, emotional and social resources originally available to the individual also play an important part. The similarities with "amotivational syndrome" (see Chapter 12) are striking.

Having previously studied young people, Hendin et al. (1987) wished to study the consequences of continued cannabis use in a group of adult habitual smokers. Subjects in a carefully selected group of 150 long-term users of cannabis were asked about their subjective impression of various effects caused by their long-term smoking. These subjects were white, did not abuse any other drugs or alcohol, and were not marginalised or socially disadvantaged. They had been using cannabis at least six days a week for at least two years. The aim of the study was to increase understanding of the role played by cannabis in these people's lives. Special interest was directed towards adaptive aspects, which were later studied in greater detail in 15 specially selected subjects.

Alongside a number of aspects subjectively felt to be positive (of which, however, some were found, in the subsequent intensive study, to be objectively negative), two-thirds of the 150 subjects felt that the main disadvantage of chronic abuse was memory impairment. Just under half were of the opinion that their ability to concentrate on a complex task had deteriorated, and an equal proportion considered that an inability to get things done was one of the negative long-term effects. Further, 43 per cent felt that there had been a deterioration in their ability to think clearly, and 36 per cent considered that their level of ambition had become lower as a result of their chronic abuse. Moreover, some of the subjects interviewed felt that acute intoxication had an additional negative effect on functions such as memory (45 per cent) and ability to concentrate (41 per cent).

An intensive study of 15 specially selected chronic abusers, which Hendin et al. carried out within a psychoanalytic frame of reference, is of considerable interest; for the main part, though, it falls outside the scope of this report. One of the findings, however, will be mentioned here. Cannabis smoking is often claimed (by abusers themselves) to have the effect of increasing one's *self-awareness* and of stimulating one to contemplate and gain a deeper understanding of one's own and other people's situation in life. The researchers were in fact struck by how consistently chronic marijuana smoking was found to have the opposite effect! Introspection was effectively inhibited, thought and feeling were separated, and the individual became less able to see reality. In other words, cannabis was used as a means of escaping from an awareness which might have provided the individual with a basis for maturing, for making conscious choices in life and for dealing with disturbed relationships.

15. Cannabis smoking in teenagers

Summary of Chapter 15

1. Cannabis smoking disrupts the hormonal balance in both men/boys and women/girls. It is suspected of being able to reduce fertility.

2. Cannabis functions as a gateway to and stimulates a transition to other illegal drugs. The hypothesis that such a causal connection exists is supported, among other factors, by the relationship that the more intensive and the longer one has smoked cannabis and the earlier one begins, the greater the risk is that one goes on to other drugs. Only recent and methodologically well-conducted studies have been able to show that, even after controlling for the effects of other known and suspected factors, there remains a strong association between cannabis smoking and moving on to other illegal drugs.

3. The development of identity, according to accepted theory and experience, is a central aspect of the psychological development of young people. In turn, the development of identity is crucially dependent on a number of other factors, including certain aspects of cognitive development, which is put at risk by long-term cannabis smoking.

4. Growing numbers of scientific studies support the opinion that the development of the immature brain is harmed when teenagers smoke cannabis.

5. A large number of clinical reports and both qualitatively focused and scientific studies of a causal association show that an early, high-level consumption of cannabis in particular causes a number of psychosocial and psychiatric problems in teenagers.

The sensitive teenage years

This is the most important chapter of this report. With most drugs – not least cannabis – the teenage years are of special importance. Vulnerability to various side-effects is generally highest in teenagers. Exposure to cannabis is also highest in the teenage years, as the early peer group takes on greater importance and a range of factors may tempt young people to "just try it".

Because the brain (mental life) is more vulnerable to toxic effects the younger the individual is, the age at which use begins is important. The general impression is that the age that use begins has dropped from the 1970s to the 2000s. This trend is clearly shown in studies from Australia (Hall W, Pacula R. L.) as well as the United States during the period 1992-2002 (referred to in Comton et al 2004), while studies from Europe do not provide the same clear-cut picture, at least not for the past two decades.

With an early start of use, both the risk of becoming dependent and the risk of psychiatric and psychosocial side-effects increase. At the same time, highly frequent abuse is more common with an early debut. The stronger marijuana has also contributed to the youngest teenagers becoming more vulnerable (W.D. Hall 2006).
For several years, it has been common for the youngest group of abusers in adolescent studies to be the 14-15 year-olds. In Fergusson's study, for example, 9 per cent of this group uses cannabis. (Fergusson et al 2002)

Naturally, most of what is discussed in other chapters applies to teenagers as well. In some cases, I refer to other sections where research findings relevant to teenagers are interspersed in chapters on harmful effects that are more focused on a diagnostic sphere than a particular age group. The following sections look mainly at those harmful effects that have specific importance in the teenage years, which often involves such effects that interact with the teenager's "developmental tasks". This is a matter of the expectations that people around them (from parents to psychologists and sociologists) tend to summarise under headings such as "breaking free from one's parents", "finding oneself ", "finding one's identity", "finding a way to relate to the other sex", "finding the meaning of life", "conquering a new social arena – from the family and teenage peer group to a circle of adults" and "choosing and starting a career". Or, quite simply, leaving – not without a certain sadness – childhood and maturing into an adult.

Database searches previously yielded no avalanche of studies that deal with this complex of problems – the teenager's encounter with cannabis abuse. Since the end of the 1990s, however, the situation has changed radically. The number of reports published in scientific articles increased during the 2000s, particularly due to scientific studies from the New Zealand birth cohorts. The situation is more troublesome with regard to the compilations of research reports mentioned in Chapter 3, which were published in book form. These reviews contain no sections on teenagers and cannabis. This is true of *Cannabis and health hazards* (Fehr K, Kalant H. editors 1983), *Cannabis: a health perspective and research agenda* (1997), and *The health effect of cannabis* (Kalant H, Corrigal W.A, Hall W. Smart R.G. editors 1999). Such a subreport is similarly missing from the large EMCDDA report *A cannabis reader: global issues and local experiences* (2008).

The health and psychological consequences of cannabis use (Hall, et al., 1994) represents an exception, where the authors discuss the issue of cannabis smoking during the teenage years in an integrated manner.

This might be attributable to the fact that it is taken as a given that cannabis is a young people's drug. It might also be that our culture's bad conscience has put blinkers on the editors and authors. Perhaps this is just another reflection of our society's inability to really see the needs of young people and to take these needs into account?

To be fair, though, it must immediately be emphasized that research teams all over the world have devoted decades to the youth-related issues. Denise Kandel and her co-workers constitute one of the best-known and most productive such teams.

This chapter will deal with four aspects of the effects caused by cannabis abuse on the teenage individual:

- Some aspects of the course of early abuse.
- Is cannabis abuse a gateway to other illegal drugs?
- Cannabis abuse and the teenager's psychosocial maturation.
- A study of the effect of cannabis on cognitive functions during adolescence.
- Studies of the significance of cannabis to young people's psychosocial development and psychiatric complications.
- The effects of cannabis on the hormonal system during the teenage years.

Some aspects of the course of early cannabis use

G.C. Patton et al (2007) monitored an adolescent cohort (1,943 participants) during ten years beginning at 14-15 years of age, i.e. from relatively early adolescence to the young adult years. The objective was to study both the *course* of cannabis and alcohol use and the *interaction* between cannabis and alcohol. In this report, I will only present a few aspects of the cannabis smokers' progression. Observations were made on eight occasions. The first was made at the age of 15 and the last at the age of 24. (Alcohol use was more common the entire time, but the difference shifted during the period of the study.) Initially (at 15 years), 8 per cent were cannabis users. From an average age of 15.5 to an average age of 17.4, the proportion of users was between 17 and 21 per cent. At the seventh observation (20-21 years), 59 per cent were users. At the last observation (24 years), cannabis use had decreased considerably, to 35 per cent.

The most important findings in this study were that different progression tendencies were distinguishable if the cannabis users were divided into "moderate" users (at least once a week) and "heavy" abusers (at least once a day): Cannabis users at an adolescent age who had moderate or intensive consumption and did not simultaneously have a high alcohol intake had a seven fold risk of being a daily user (i.e. virtually dependent [my comment]) at a young adult age. In this kind of abuse/dependence established early on, cannabis abusers had a lower level of social function than the alcohol abusers from the same cohort. Moreover, they ran a markedly elevated risk of shifting over to other illegal drugs at a young adult age.

Is cannabis abuse a gateway to other illegal drugs?

The question of whether cannabis represents a gateway to other illegal drugs has occupied clinicians and researchers for 40 years. The reason for the interest in this question has been that a transition to other illegal drugs – heroin, amphetamines

or cocaine – represents an increase in the degree of risk to which the individual is exposed. Even though cannabis is more psychopathogenic than heroin, intravenous heroin abuse is in many other respects a different kind of serious condition than cannabis dependence. With heroin, which is also much more expensive than cannabis, addiction often develops quickly, the dependence is strong, and mortality is considerably higher, mainly owing to overdoses. It is the rule rather than the exception that heroin-dependent individuals become socially marginalised. The abuse of both amphetamines and cocaine (not least in the form of "crack") also leads to rapid development of severe dependence, with the risk of a series of mental side-effects and high mortality levels. Moreover, transition to intravenous abuse adds the risk of HIV infection. Although cannabis is not a lethal drug, it is misleading to call it "light" and others "hard". It sends the wrong signals to young people. This entire report concerns the harmful effects that are partially or entirely caused by cannabis.

The most extensive early studies in this field have been carried out by Denise Kandel and her research team. They showed, at an early stage, how young people in the United States tended to progress through a sequence of increasingly stronger drugs. A very large proportion of their subjects followed a series of graded steps, and very few deviated from the progressive sequence or hierarchy expected. The researchers identified four stages: 1) beer and wine; 2) cigarettes and spirits; 3) marijuana; and 4) other illegal drugs (Kandel, 1989). They also found that the younger the age at which abuse started, the higher in the drug hierarchy the individual would climb; and the more intensive the abuse at any given stage, the greater was the risk that the individual concerned would progress to the next stage. Research carried out in the Nordic countries has found similar tendencies (Aas & Pedersen, 1993). Golub and Johnson (1994) have shown how the importance of alcohol as a gateway to abuse of other illegal drugs has declined while that of marijuana has increased. This is considered to be due primarily to the strong expansion of marijuana smoking observed in the United States up to the beginning of the 2000s. Yamaguchi and Kandel (1984) have also shown how extremely rare it is for more advanced drug abusers *not* to have progressed via marijuana. Here, though, it should be emphasized that it is only a small fraction of those who smoke cannabis that ever try other illegal drugs, and even fewer who continue using such other drugs.

In general, then, prior cannabis use seems to be a necessary condition for the transition to other illegal drugs; but is cannabis also a gateway to other illegal drugs in the sense that cannabis abuse is actually the cause of heroin, cocaine or amphetamine abuse? A great deal of effort has been devoted to answering this question. Since the vast majority of cannabis smokers do not become abusers of other illegal drugs, there is no simple causal connection. What we can conclude from the various studies is that cannabis is only one of the factors that seem to predispose an individual to the abuse of other illegal drugs. A range of other negative social and psychological background factors are also very important.

Kandel et al. (1986) demonstrated a direct association between the intensity of cannabis abuse and the risk of progression to other illegal drugs. Of the subjects in their study group who had used marijuana more than 1,000 times in the course

of their lives, 90 per cent had also tried other illegal drugs. Of those who had used marijuana between 100 and 1,000 times, 79 per cent had used other illegal drugs, and of those who had used marijuana fewer than 100 times, but more than 10 times, 51 per cent had used other illegal drugs. Of those who had used marijuana between 1 and 9 times, 16 per cent had also used other illegal drugs. Among the subjects who had never used marijuana, though, only 6 per cent had used other illegal drugs.

This statistical association between the intensity of cannabis consumption and the likelihood of using other illegal drugs strengthens the case for assuming that there is a causal connection between cannabis smoking and progression to other illegal drugs, but it does not constitute proof of such a causal connection.

Kleber (1995) has pointed out that studies from the Center on Addiction and Substance Abuse at Columbia University have shown that 60 per cent of the young Americans who use marijuana before the age of 15 will use cocaine later in life. Further, it has been shown that young Americans between the ages of 12 and 17 who use cannabis are 85 times more likely to use cocaine than those who do not smoke cannabis.

In other words, it appeared as if the "gateway theory" could not be proven scientifically. On the other hand, a large body of circumstantial evidence has been gathered. It is found time and again that cannabis is a central component of the network of influencing factors that leads to the abuse of other illegal drugs.

Some people claim that this is the crucial question of the debate on the dangerousness of cannabis: "If the gateway theory is incorrect, cannabis cannot really be all that dangerous, can it?" The intensity of the defence of the gateway theory has often been based on the assumption that the accuracy or inaccuracy of this theory determines what the correct view on cannabis should be. Since I account for many other suspected or proven harmful effects of cannabis abuse in this report, I obviously do not share that assumption.

Has the question of the role of cannabis as a gateway to other illegal drugs been answered?

Fergusson et al (Fergusson, et al., 1997, 2000, 2002, 2005, 2006) are monitoring a cohort of New Zealand children/adolescents/young adults (Christchurch's birth cohort). These researchers have a unique knowledge of the children and their background, which makes it easier to identify co-variant variables. On one hand, they are studying background factors and cannabis abuse and, on the other, a number of psychosocial and psychiatric problems. One of the conditions studied was the young people's transition to other illegal drugs and whether or not there was a causal association with cannabis abuse.

At the time of the first analysis, the subjects were 18 years old. Like many researchers before them – not least Kandel's team – Fergusson et al. found that the initial analysis showed associations which were not, when other known factors were controlled for, very strong at all. The researchers then joined above all Kandel, but many other researchers as well, in suggesting an alternative explanation.

As the young people came into contact with cannabis, the researchers claimed, the effects caused by cannabis on the mind, the culture surrounding the drug, new friends who had acquaintances in abuser circles as well as other circumstances all combined to amplify the impact of negative background conditions. This hypothetical process is called a "cascade effect" (Kandel et al., 1986). In this way, then, cannabis would indirectly have caused or contributed to a number of difficulties encountered by the young people, including progression to other illegal drugs. This was obviously bad enough in its own right, but there had been no convincing proof that cannabis constituted a specific causal factor.

At the time of the later analyses, the subjects were 21 years old. The researchers then had more data at their disposal and used more advanced methods of analysis. It was possible not only to take more careful account of other factors known to contribute to negative developments, but also to control, to a degree, for time-dependent and not fully known influencing factors. The more intensive the cannabis abuse, the stronger was the association with use of other drugs. For younger (14–15 years old) large-scale consumers in particular, there was found to be a very strong association even after controlling for other known or suspected co-variant factors (Fergusson et al., 2002).

Here, then, a different picture emerges. Cannabis abuse is here an independent specific factor, in all likelihood a cause of the progression to other illegal drugs. A strong connection between cannabis use on one hand and a negative effect on the other encourages the consideration of some type of neurophysiological process rather than the psychosocial mechanisms generally nearby. Accordingly, an interesting line of research with accompanying hypotheses deserves being mentioned. This relates to the phenomenon of sensitisation (Swedish National Institute of Public Health 1999), a sort of "inverse tolerance effect" where an addictive substance increases a person's sensitivity to the euphorising effects of that substance. Not least interesting is the occurrence of cross-sensitisation. This means that exposure to one preparation (e.g. cannabis) should be able to make a person more sensitive to another preparation (e.g. opiates). This very effect has been shown in animal experiments (Maria Ellgren 2007).

Since Fergusson and his co-workers conducted their studies, they have found further support for their conclusions through two twin studies, one in Australia and one in the Netherlands. Both research teams were led by Michael Lynskey. The objective of the study in Australia was to investigate the gateway hypothesis by using pairs of twins. One twin was an early user of cannabis, and the other was not. The difference (cannabis abuse) could be singled out by the researchers using twins who had grown up together and were also "controlled" in a customary manner. Even though the twins had so much in common, the twin who had begun smoking cannabis before the age of 17 had a significantly greater risk of making the transition to other illegal drugs than the twin who did not smoke at all or had begun after the age of 17.

One common argument to explain why the cannabis smoker moves on to other illegal drugs is that being a cannabis abuser, especially with an early beginning, one automatically comes into contact with the circles where other illegal drugs are used. The transition to these drugs then becomes the result of social interaction and not an expression of an acquired need in the cannabis abuser (such as through sensitisation as described above).

One of the reasons for the legalisation of cannabis in the Netherlands was the desire to break the connection that existed (there as in other countries) between the handling of cannabis and the sale and use of other illegal drugs. Lynskey therefore conducted a similar study in the Netherlands with Dutch colleagues (Lynskey et al 2006). The results were similar to those found in Australia, however. The early cannabis-smoking twin had a risk of beginning with other illegal drugs that was 16.5 times greater than the other twin. Accordingly, it is not very likely that the cause could be the social integration between cannabis environments and other illegal drug environments, since it does not exist in the Netherlands.

Cannabis abuse and the teenager's psychosocial maturation

Cannabis abuse and cognitive development during the teenage years

In Chapter 14, there is a discussion of the effects caused by long-term cannabis abuse on cognitive functions. From that discussion, it is clear that cannabis smoking has negative effects on a number of aspects, not least aspects which are of importance for more complicated thought operations, such as planning and the integration of impressions and previous memories. Memory disorders are the most common cognitive impairment. It is worth repeating here that short-term memory is also called working memory, and that it is not just a "memory function", but a central location for the coordination of a number of mental functions which play an important role in enabling individuals to orient themselves relative to the surrounding world, such as planning, reorientation and reacting to new and unexpected circumstances. The scientific studies and clinical observations previously referred to concerned mainly adults; here we will look at what these kinds of cognitive disturbances can entail for teenagers, who are in a dynamic developmental phase.

In order to emphasise that teenagers are at least as sensitive as adults to the effects produced by cannabis on cognitive functions, I would like to refer to a study which was carried out on teenage subjects. In a very thorough study, Schwartz (1989) showed that long-term cannabis smoking at the relatively high THC concentrations (7 per cent) which were used as early as the late 1980s in the United States led to a significant reduction in the short-term memory of the subjects. It is particularly noteworthy that memory impairment remained six weeks after use ended. The findings are in line with the studies mentioned in Chapter 14 which showed that "residual effects" on cognitive functions persisted for a time after the abuse had ceased.

Identity development, formal thinking and cannabis abuse

In this section, I deviate – for reasons which I hope will be obvious – from the structure found elsewhere in this report. By means of a slightly more extensive discussion based on qualitative studies, I try to place the study findings to which I refer in a larger context.

Baumrind and Moselle (1985) maintain that many studies are not only deficient in terms of methodology, but also lack a theoretical foundation. With this type of research on complex relationships, it is necessary for studies to be based on an explicit theory of teenage development. This is necessary for the researchers to be able to formulate hypotheses, ask relevant questions and choose adequate study instruments. Without such a theoretical foundation, there is a risk that the studies will produce a bulk of disconnected statistical data which are difficult to deal with. Having indicated some of the ways in which propitious youth development is made more difficult in the society of the 1980s, the authors go on to describe, stage by stage, the development which occurs during the teenage years. Baumrind and Moselle see a progressive transformation of "action schemas" from less integrated to more integrated systems as being the central thrust of youth development. They describe the manifestations of the maturation process within a range of different psychosocial categories. As in the psychoanalytically oriented development theories, the forging of a personal identity is a central element of this model. In this regard, this model resembles in several ways my own lines of thinking on the importance of social integration to the development of identity in the late teenage years (Ramström, 1991). In this context, we can also remind ourselves that several researchers from various disciplines have emphasised that the environment in which the teenagers of the Western industrialised societies of the 1980s and 1990s are to mature into adulthood seems to be hazardous in certain respects (Ramström, 1991; Ziehe, 1986; Lasch, 1983). If this is so, drug abuse which makes this maturation process more difficult, or delays it, takes on an even greater importance.

Given our knowledge that cannabis produces negative effects on cognitive and other functions, it is of considerable interest to note that Baumrind and Moselle, like Steingart (1969) and Ramström (1991), consider that certain stages of cognitive development – especially the ability for abstract thought – are crucial to the development of identity in the teenage years. According to Piaget, the child's ability for concrete thinking is supplemented by the ability to perform formal thought operations at the age of 11–13 (though it has later been questioned whether this stage does not in fact normally occur somewhat later, at the age of 15–16). The ability to perform formal thought operations is the basis of the ability for abstract thought. At this stage, unlike during the period of concrete thinking, the young person is able to conceive of a world different from the actual reality before his or her eyes at any given moment. It is this development that enables the child to re-evaluate his or her parents' way of being, not rarely causing them pain.

But the ability for formal thinking also provides the foundation for long-term planning of the development of one's own personality. Once an individual has

reached this stage of cognitive development, he or she can move on from the kind of planning typical of the child ("When I grow up I'm going to be a millionaire") to a kind of planning that reflects the increasing maturity of the adolescent ("By choosing a certain study programme at upper-secondary school and working to achieve certain grades, I can acquire the education I need for entry to the career that I want"). There is strong evidence that the functional shortcomings described in Chapter 14 as being characteristic of cannabis abusers are largely related to an inadequate ability to perform formal thought operations (Lundqvist, 1995a).

If the development of identity does not progress, the teenager remains at a childish level of development characterised by both a lack of independence and deficient integration in the adult world.

By placing our knowledge of the mechanisms by which cannabis produces its effects, mainly as regards its impact on cognitive functions, in relation to a central and crucial element of the mental development of the teenager (the forging of identity), we can thereby see how prolonged smoking of hashish during the teenage years may result in a stagnation of psychosocial development. Still, even though the interaction just described affects the core of teenage development – the forging of identity – and is therefore very important, we must not forget that the impairment of mental functions can have a range of other effects. Deterioration of short-term memory obviously makes learning more difficult, but it also has a negative effect on the individual's ability to make plans, establish new relationships and make realistic assessments of the world around him or her.

In recent years, researchers have also found that the consumption of cannabis in the early teenage years has a causal connection with mental and social disturbances in the later teenage years and early adulthood. Quite a few of these disturbances have been mentioned already: psychosis (Arseneault, 2002), depression and suicidal thoughts (Bovasso, 2001; Patton et al., 2002), and criminality and unemployment (Fergusson & Horwood, 1997; Fergusson et al., 2000; Fergusson et al., 2002).

A study of the effect of cannabis on cognitive functions during adolescence

We must also avoid forgetting other approaches. We know from neurophysiology that adolescence is a period in which the brain's morphology and complicated communication system are still undergoing significant morphological and neurophysiological changes. The thought that this, in all likelihood, involves a period of greater vulnerability to cannabis abuse is supported by a study by K.L. Medina et al (2007): They compared 31 cannabis abusers in the ages of 16-18 with the same number of control subjects. After four weeks of monitored abstinence, a battery of tests was presented that focused mainly on cognitive functions and some psychomotor tests. The cannabis group showed clear functional impairments. A connection was found when the evident degree of functional impairment was later compared to the number of cannabis episodes. The more episodes, the greater the functional impairment was. The research group found it reasonable to assume that the cognitive damage was caused by smoking cannabis. Most similar studies of adults have shown

similar functional impairments, but with effects that subsided after less than four weeks and a weakening after just a few days (H.G.Pope et al). If these changes really become permanent (and were not present before the smoking began, which the relationship of the damage to the degree of exposure and the careful selection support), it constitutes support of earlier observations, including functional disturbances. It is feared that THC affects – by disrupting and delaying – the cerebral maturation process that is not complete until a few years after the age of 20.

Clinical experience

In addition to accounts given of their experience by field-workers, doctors and nurses, teachers, police officers and not least parents, there are also more systematised and detailed descriptions of the long-term effects produced by cannabis on teenagers – for example textbooks (Heinemann, 1984; Ramström, 1987), a section of a research report (Lundqvist, 1995) and a clinical report in a scientific journal (Kolansky & Moore, 1971). Kerstin Tunving, a very experienced doctor in the field of drug-addiction treatment, wrote the following in her article *Psychiatric Aspects of Cannabis Use in Adolescents and Young Adults* (1987):

> To sum up, the impression is, based on clinical observations, that teenagers who abuse cannabis "sleep away" their teens. They often do not develop at the same pace as youth of the same age, but stay childish and dependent.

It is also of interest to note that what induced Richard Schwartz and his co-workers to conduct a study into the effect of cannabis on short-term memory in young people was, in fact, repeated clinical experience of cannabis-dependent young people who, when admitted to a treatment programme, found it very difficult to remember information and instructions during the first three or four weeks.

Early scientific studies

In the introductory chapter of their large study *Living High*, Hendin et al. sum up their findings from earlier studies of cannabis-smoking teenagers:

> In all of its functions marijuana served to detach these adolescents from the problems of the real world – from their anger and unhappiness with their parents and from the need to work and compete to achieve success [...] Fantasies of being destined for a special fate, to become rich without work, and to excel at a sport they scarcely played were typical of the parody of success, achievement, and confidence that marijuana sustained in some of the young men […] The young female marijuana abusers, although not usually expecting particular greatness, nevertheless maintained a magical belief that good things would happen to them: college acceptance while flunking out of high school, or happiness in love

> while dating unresponsive or abusive young men. For all these adolescents, marijuana helped sustain in an unrealistic way the desire for power, control, achievement and emotional fullness (Hendin et al., 1987, p. 14).

In her dissertation The Prognosis of drug abuse in a sixteen-year-old population, Maj-Britt Holmberg (1981) studied over 1,000 Swedish pupils in the ninth year of school (aged 15–16). Of these, 14 per cent used cannabis (primarily). At a follow-up after eleven years, she found the following:

- The mortality rate was 5–8 times higher among those who were abusers at the time of the first interview in the ninth year of school.
- The abusers (together with those who had attended remedial classes or had left school prematurely) had had an above-average level of medical and social problems during their childhood and youth.
- Of the drug users, 10 per cent had been diagnosed as having a psychosis during the eleven-year follow-up period.
- The 2.4 per cent who had claimed a highly frequent use of drugs (with cannabis being the dominant drug) were more likely to develop drug addiction proper than the other abusers.
-

The most extensive and in-depth longitudinal study of young cannabis smokers carried out at the time was conducted by Michael Newcomb and Peter Bentler (1988). In their main report, they concentrate on the effects of cannabis use on individuals' entry into young adulthood. They studied the consequences of use/abuse of alcohol, marijuana abuse and the abuse of other illegal drugs. In many respects, the three categories of drugs produced similar effects.

The findings reported include the following:

- Cannabis smoking increased the risk of impairment to mental functions in young adulthood. The researchers measured a higher degree of "psychoticism" and a reduced ability to make careful plans. "This effect […] indicates that teenage drug use interferes with organized cognitive functioning and increases thought disorganization into young adulthood."
- Only the use of other illegal drugs was found to be associated with an increase in suicidal thoughts during young adulthood. (See, however, the above section on the risk of transition from cannabis to other illegal drugs.)
- Smoking cannabis as a teenager was shown to have a clear association with a number of negative psychosocial factors during the teenage years, but above all during the early stages of adult life. The abusers in

this study, like those in e.g. Kandel's (1986) study, were more likely to interrupt their training or education. Once they reach adulthood, abusers exhibit less stability on the labour market – i.e. they find it harder to hold down a job.

- Further, the abusers showed a significantly stronger tendency to fail in their marriages, as expressed in a higher divorce rate.
- Finally, it was found that the social networks built by the abusers during these early years of their adult lives were worse than those of the non-abusers.

Newcomb and Bentler (1988) conclude that their large-scale study supports, in a number of respects, Baumrind and Moselle's theory that abuse (of e.g. cannabis) during the teenage years leaves teenagers less well equipped to integrate themselves into adult life.

Scientific studies from the 2000s

In a review, W. Hall (2006) emphasizes that the young abuser runs an extra large risk of becoming *dependent* (see Chapter 5), a risk that is larger the earlier use began. Being dependent in turn mainly increases the risk of the following harmful effects: *a transition to other illegal drugs* (see the gateway discussion above), *poor performance in school*, *including extensive truancy and early dropouts* (Lynskey M., Hall W. 2000) and *of being affected by psychotic symptoms*.

The young people with high levels of consumption also run a not insignificant risk of depressive symptoms and, above all, *acts of suicide*. (See Chapter 11, "Affective disorders".)

It is clear that many of these early harmful effects change and become worse in later adolescence and result in problems in the transition from being a child to young adulthood, if the abuse continues. Here are a few examples: with continued high-level abuse, the connection between cannabis and other illegal abuse becomes even clearer (Fergusson et al 2005). In late adolescence, some of these young people have both amassed a high total dose of cannabis and developed psychotic symptoms, two precursors to schizophreniform disorders (van Os et al 2002, and Chapter 9, "Cannabis smoking and schizophrenia"). Also refer to Patton's sequential study in this section.

The effects of cannabis on the hormonal system during the teenage years

As is shown in Chapter 20, cannabis can affect the hormonal balance in both men and women. The changes in hormonal balance which cannabis can provoke are suspected of being involved in a relative reduction of fertility in men. There is reason to suspect that such hormonal effects may be more important during puberty than later on in life. In the 1970s and 1980s, occasional reports were published that the

low level of testosterone could also cause other symptoms, including an occasional case of general feminisation (Hollister 1986).

In women, the menstrual cycle is affected. Taken together with findings from animal experiments, this is considered to suggest that cannabis can bring about a relative reduction of fertility in women as well.

To sum up, we know that continual cannabis smoking disrupts the hormonal balance of the body. The effects of this disruption include a lowering of testosterone levels in men/boys and disturbances to the hormones which control the menstrual cycle in women/girls. We do not know exactly how this affects teenagers, but the suspicion is that it can reduce fertility in both sexes. If so, this becomes particularly significant for those who already have reduced fertility for other reasons.

16. Cannabis and driving

Summary of Chapter 16

Experimental studies show that cannabis smoking has a negative effect on a number of mental functions (psychomotor and cognitive), which are of importance for driving.

Studies making use of both simulators and real driving situations with and without traffic show how cannabis, even in moderate doses, impairs the ability to drive a car.

A number of well-done epidemiological studies have confirmed the experimental studies. Among other findings, it has been shown that a driver's THC level in the blood is directly related to the risk of causing a traffic accident. One well-known review of such studies shows that a person who has consumed cannabis has a 3-7 times greater risk of causing an accident than somebody who is not under the influence.

Both experimental studies and epidemiological studies show that cannabis combines with alcohol in a synergy effect causing a dangerous influence on the driver.

In attempts to map the circumstances that increase the likelihood of "driving a motor vehicle under the influence of cannabis", the following factors were identified:

- cannabis dependence/cannabis abuse
- poly-drug abuse
- ignorance of the risks of cannabis in traffic.

Introduction

What is said in this chapter with regard to driving a car naturally also applies to the driving of a bus or a train, and to an even larger degree with regard to the piloting of an aircraft. Further, it seems reasonable to assume that demands similar to those placed on a driver are made of persons required to operate certain machines/appliances used in modern processing industry, and also, in certain aspects of their work, of those employed in certain other professions, such as doctors, nurses and air-traffic controllers.

The focus here is not on the negative effects caused by daily or near-daily abuse on intellectual performance in general; what is discussed in this chapter are the immediate (and residual) effects which cannabis intoxication has on mental functions of importance for driving, primarily within the sphere of cognitive and psychomotor functions. These effects seem to be roughly the same irrespective of whether the cannabis user is a beginner or a habitual smoker. For intensive smokers, though, there are additional effects from the generally significantly higher doses due to repeated

storage of THC with continued smoking. Even during interruptions in use, residual effects – particularly those impacting the cognitive functions – remain significantly longer for intensive smokers.

The effects of cannabis intoxication on individual psychomotor and cognitive functions

As is explained in the description of cannabis and THC given in Chapter 2, cannabis intoxication produces, alongside euphoric effects common to many drugs of abuse, a cannabis-specific effect on cognitive functions (perception, temporal understanding, short-term memory and attention) and motor functions (coordination, etc.). I will begin this section with a very condensed overview of the central components of the research that has focused on functions considered to be most important for the ability to safely operate motor vehicles in traffic.

Herbert Moskowitz – one of the leading researchers in this field – presented a wide-ranging review, extending up to the mid-1980s, of scientific studies that deal with the acute effects of cannabis, focusing in particular on driving (Moskowitz, 1985). He maintains that, beyond all doubt, cannabis, even in moderate doses, impairs functional ability with regard to *coordination*, *tracking* (i.e. the ability to rapidly follow, by means of an instrument, an irregularly moving object), *perception* and *vigilance* (the ability to pay attention).

He also accounts for a number of studies demonstrating a deterioration of the ability to judge the length of an interval of time as well as a deterioration of short-term memory. The latter is the most constant finding in studies of the acute effects of cannabis intoxication (Miller & Branconnier, 1983). However, Moskowitz expresses some doubts, not least based on several of his own studies, as to the importance of these two functions for driving. On the other hand, Leirer et al (1991) have shown that a correctly functioning short-term memory is crucial for an aircraft pilot, who has to carry out a series of interconnected actions (and remember where in the series he or she is!) both while flying and during take-off and landing. Leirer also emphasizes that car drivers have the same requirements of functioning cognitive resources in difficult traffic situations.

With regard to a few other functions, reaction time being one example of major importance for driving, the findings were uncertain. Later, Wilson et al. (1993) did, however, demonstrate the existence of a clear association between a more realistic dose of cannabis (15–35 mg) and reaction time.

Studies of the ability to drive when under the influence of cannabis

The findings described above only show how cannabis affects individual functions. With regard to judging the traffic risks, if any, posed by cannabis smoking, a more important contribution has been made by the studies which have assessed the direct effect caused by cannabis intoxication on individuals driving cars or using car-driving simulators.

In this context, the following kinds of study have been carried out:

- studies using a driving simulator
- studies using a flight simulator
- experimental studies of intoxicated persons driving a car:
  - on a test track free of other traffic
  - in traffic.

Simulator studies

An overall assessment of simulator studies carried out up until the mid-1980s is included in Moskowitz's research review. The studies conducted in driving simulators show both a reduced ability as regards direct control of the car and a deterioration of the ability to make correct interpretations of visual and auditory input which is of importance when driving. In one study, whose participants included Moskowitz, the researchers suddenly introduced an obstacle which entailed a collision risk. At higher doses of THC, several subjects were unable to avoid a crash (Smiley, 1986).

The flight simulator is considered to be the most sensitive instrument for laboratory studies of the relationship between humans and complex machinery, and the effects caused by various drugs on this relationship. In certain respects, of course, flying an aircraft is a more complex task than driving a car; but since the laboratory situation probably entails, in several respects, an underestimation (see below) of the effects caused by the drug compared with real-life situations, the findings of flight-simulator studies should be seen as providing an important contribution to our understanding of the risks involved in driving. Naturally, these studies are carried out on experienced aeroplane pilots.

Janowsky et al. (1976) – also mentioned by Moskowitz – tested the ability of pilots who were under the influence of cannabis to carry out various sequences of actions typical of instrument flying. Even though the dose of THC given was low (8 mg), the pilots showed clear functional impairment, which appeared to be due above all to reduced short-term memory. Leirer et al. (1991) conducted a well-known flight-simulator study using higher – but still very moderate – doses of THC (20 mg). They had nine test subjects, all experienced pilots, and a control group. The nine test pilots' performance deteriorated in several respects, during flight as well as during take-off and landing. The researchers also found moderate but significant (and in a real-life situation hazardous) impairments as long as 24 hours after the administration of cannabis. This was several hours after THC ceased to be of measurable concentrations in the blood. None of the pilots felt that they were still under the influence and only one of them perceived that diminished functionality remained after 24 hours. The research group realised that, even though it is significantly more complicated to handle an aircraft than a car, a similar situation – with residual effects 24 hours after smoking – could also arise in an automobile traffic

situation. This could, for instance, arise in an extreme situation with difficult traffic or weather conditions.

Remarks on the older studies: One of Moskowitz's (1985) conclusions is that almost all the studies referred to used comparatively low doses of THC. Thus, the effect produced by more "realistic" doses could be considerably larger.

Studies of driving on test tracks and in traffic

In three studies (Hansteen, 1976; Klonoff, 1974; Attwood et al., 1981) of car driving on tracks free of other traffic, it was found that cannabis caused slight to moderate impairment to driving ability. One of the studies also looked at driving in traffic, but the findings made were inconclusive. In all of these cases, however, low or very low THC doses were used.

Robbe (1994) carried out an extensive research programme whose central focus was car driving, both on a closed-off road and on a motorway with normal traffic. The subjects in one study group (people who smoked cannabis more than once a month but not on a daily basis) were instructed to experimentally determine their optimal dose for "getting high", and the average of what they found was used to set the highest dose given in the experiment at approximately 20 mg (300 µg/kg body weight). This is probably a relatively low dose: habitual smokers can consume 200 mg, and sometimes twice as much, in one day (Moskowitz, 1985); and with the strong varieties of marijuana in use today, a single 1-gram cigarette can contain up to 200 mg THC.

Robbe's study shows that cannabis smoking causes a significant deterioration of driving ability. The most sensitive of the factors studied – influenced at all three dose levels used: 7, 14 and 20 mg – was the *standard deviation of lateral position* (SDLP). This is a variable which has previously been used in studies of the effects on driving of alcohol and other drugs, and it is a function of the ability to keep the car steadily in the middle of the lane at a constant distance from the verge of the road.

Results were obtained only for driving on a road free of other traffic. In the experiments carried out on roads with other traffic, only the lowest dose (6–7 mg) was used (for safety reasons), and at that dose no significant impairment of driving ability could be identified.

Comparisons were made with identical studies concerning the effects of alcohol on driving ability. The SDLP deviations recorded for the 20 mg dose were very close to the deterioration in the same variable observed in persons with a blood alcohol level of 1.0 grams per litre. Robbe summarises that his studies confirm previous studies carried out using driving simulators and experimental driving on traffic-free roads: *Cannabis in moderate doses impairs the ability to drive a car*.

Presence of cannabis in the blood of drivers involved in road accidents – culpability studies

It has proved very difficult to carry out studies relating to the presence of cannabis in the blood of victims of traffic accident and to draw any firm conclusions from such studies, in particular those which were carried out a few years ago. The main reasons are problems concerning legal aspects, practical difficulties (above all relating to measurement techniques) and issues of research methodology. At one point, it seemed that the most fruitful approach in this field of research was to calculate a "culpability index", an index of the degree of culpability. In a group of drivers involved in accidents, those who were under the influence of cannabis and those who were not were compared with regard to the extent to which they caused the accident. Warren's study (1981) found that, if the risk index of drivers not under the influence of cannabis was set at 1.0, that of cannabis-intoxicated drivers was 1.7 – the same risk index as for drivers under the influence of alcohol. In other words, this study showed that a driver under the influence of cannabis was almost twice as likely as a non-intoxicated driver to cause a serious road accident.

Certain other studies, however, have failed to find the same type of association; and in general, this method has yielded contradictory results. According to Ramaekers, this is probably due, among other factors, to the fact that not all researchers have measured the level of the relevant substance, but tested instead for non-psychoactive metabolites which are irrelevant to an assessment of the *current* influence of cannabis (consumption during or within a few hours prior to the journey). The problem is that these metabolites (above all THC-COOH) remain in the body for much longer than THC itself. While the presence of such metabolites obviously indicates earlier consumption of cannabis on the part of the individual, this consumption may have taken place several days before the time of driving. Incidentally, Ramaekers advocates – due to several methodological and practical difficulties – a return to a more traditional type of study where the drivers that caused accidents are compared with an appropriate control group.

Presence of cannabis in the blood of drivers involved in road accidents – case-control studies, etc.

In a systematic review of earlier studies using more modern analysis techniques and traditional methods (case-control studies), Ramaekers et al. have found that there is in fact a stronger link between cannabis consumption before (or during) driving and an increased risk of accidents than there was previously thought to be. These studies found that drivers under the influence of cannabis were three to seven times more likely to be the cause of an accident in which they were involved than were drivers not under the influence of cannabis or alcohol. In his review, Ramaekers also emphasises that both experimental and epidemiological data clearly show that the combination of cannabis with alcohol strongly increases in the risks associated with driving. In this context, he refers to a study carried out by members of his team (Ramaekers et al., 2004), showing that the combination of clearly moder-

ate amounts of alcohol with moderate amounts of cannabis caused a very strong increase in the risk of making mistakes while driving.

A noted French study (Mura et al., 2003) compared blood samples from 900 car drivers who had sustained injuries as a result of road accidents with blood samples from 900 control subjects. The control group consisted of patients who had been transported to or sought help at the same emergency ward as the road-accident victims, but for reasons other than traffic injuries. The control subjects also had driving licences.

One of the findings made was that the most frequent "drug" was alcohol, which was detected (at a level above the French legal limit of 0.5 g/litre) in 26 per cent of the drivers (and in 9.5 per cent of the controls). For cannabis alone, the proportions were 10 per cent for the drivers and 5 per cent for the controls.

In the youngest age group (18–27 years), the corresponding figures for alcohol were 17 per cent of the drivers and 6.7 per cent of the controls. The corresponding figures for cannabis alone (i.e. no other drug nor alcohol present), the proportions were 14.1 per cent for the drivers and 6.7 per cent for the controls. For the group with a combination of THC and alcohol (> 0.5 g/litre), these figures were 9.5 per cent for the drivers and 2.2 per cent for the controls. If, like the researchers, the higher percentages of THC in the blood are viewed as causal factors, the following increase in the risk of having a traffic accident is found in the young age group (with the most significant differences):

Only cannabis	2.5 fold greater risk of road accident
Cannabis and alcohol	4.6 fold greater risk of road accident

In 1999, prior to a possible change in narcotics legislation, the French Government wanted reliable epidemiological data mainly on the role of cannabis in road accidents in France. The research project that was organised comprised suitable medical centres throughout the country and lasted two years beginning in October 2001. The project focused on all traffic accidents that resulted in an immediate fatality. All of the drivers were examined to see if they had alcohol or drugs in the blood. The study group consisted of drivers who had caused accidents (including those who had died in the crash) and comprised 6,766 individuals. The control group consisted of 3,006 drivers who neither caused the accident nor were victims in the crash. For the control group to be as representative as possible of "the general population of drivers", standardisations were done against another large, identifiable driver population in France.

Of the study group, 8.8 per cent were found to have THC in their blood. Among the control subjects, 2.8 per cent had THC in their blood. Cannabis intake prior to or during the journey resulted in an average risk increase of 3.32. The risk was clearly dependent on the measured level of THC in the blood (i.e. the risk was dose dependent). If the blood content was a minimum on the measured scale of < 1 ng/ml, the risk was 2.18. If the level was the highest on the scale > 5 ng/ml, the risk was 4.72, i.e. nearly five fold.

It can be added that, at the time, the total proportion of accidents estimated to be caused by cannabis in France was 2.5 per cent. At the same time, alcohol caused 28.6 per cent of the traffic accidents.

The association between different smoking habits and the risk of having a traffic accident

Goodwin et al conducted a retrospective study of a large representative group (a cohort that comprised 64,500 people) within the framework of the Northern California Health and Care Program. In 1986, the group had been interviewed with regard to health-related behaviour (including alcohol habits, drug use, hospital stays and so on) during the period 1979-1985. The researchers compared the extent to which cannabis users/abusers and non-users were cared for in hospital after traffic-related injuries during the ensuing five years. Male cannabis users had a 2.3 times greater risk than non-users of being involved in a traffic accident followed by hospitalisation (Goodwin et al 2003).

In the Auckland district of New Zealand, S. Blows et al conducted a study on the relationship between habitual smoking (> once/week for the past 12 months) and being involved as a driver in a car accident with at least one injury or fatality. All traffic accidents with an injury or death occurring over an 18 month period were recorded. The drivers constituted the study group. During the same period, a control group was gathered through the recruitment of drivers straight off the road with a randomised coverage of the districts road network. They strived to gather the control group at the same times of the day and year, and in the same numbers per stretch of road to match the study group.

The 527 drivers in the study group and 588 control subjects were interviewed regarding their personal circumstances, circumstances that could affect driving risk and current conditions (at the time of the accident or at the time the control subject was recruited) such as fatigue, seat belt use and so on. Measurements were taken of the alcohol content in exhaled air.

Two "cannabis questions" were asked: 1. **Current intake.** Whether the driver had consumed cannabis within three hours prior to the accident or before recruitment of the control group driver on the roadside. 2. **Habitual smoker.** If the driver was a habitual smoker (as defined above) of cannabis.

Findings: The significant difference found between the groups with regard to "current intake" disappeared after controls for co-variant factors. On the other hand, a significant association (risk index 9.5) remains between being a "habitual smoker" and being involved in a serious traffic accident. The researchers emphasized that the relationship between cannabis abuse and "risk-taking behaviour" should be the subject of further study. Further, they believe that their findings indicate that intervention efforts (prevention or treatment) should be focused more on high-consumption groups (S. Blow et al 2005).

Driving under the influence

A decisive phase of the series of events that can lead to a traffic accident is of course that somebody who is under the influence of cannabis gets behind the wheel of a car or mounts a motorcycle and drives under the influence. To find out more about the origins of this risk situation, many studies have been conducted to answer the following questions: *How common is it? Is this a common behaviour of the cannabis user or mainly someone who is dependent? Why do people drive under the influence; is it ignorance, a part of a general asocial pattern of behaviour or something else?*

Conditions differ significantly across different countries, even within Europe, as well as between different groups within the same country. The factor of most interest – what it looks like in the average population – is probably the most difficult to provide answers on. The following subgroups and behaviours are of particular interest in this context:

- habits among various groups of cannabis abusers
- habits among the generally most injury-prone group among motor vehicle operators: younger men
- Blood THC levels in those suspected by the police, based on behaviour in traffic or personality traits, to be under the influence of a substance other than alcohol.

"Driving under the influence" is probably a rare occurrence in the average population. In the study by Laumon et al presented above, they found that the prevalence in France at the beginning of the decade was 2.8 per cent (Laumon et al 2005). In the Netherlands during the period 2000-2004, 4.5 per cent of a randomly selected group of car drivers in a police district were found with a blood test to have taken cannabis (Drugs and Driving 2007).

In a survey of 6,000 young people aged 16–19 based on anonymous telephone interviews (Hingson et al., 1982), it was found that driving a car after either drinking alcohol or smoking cannabis increased the risk of being involved in a road accident. Those who drove after smoking marijuana at least six times a month were 2.4 times more likely to have a road accident than those who never drove after smoking cannabis.

In Castillo y Leon – Spain's largest region with several major cities, villages and extensive rural areas – 2,500 residents were studied in 2004 with interviews regarding cannabis smoking, car driving and a large number of social factors. Of these subjects, 15.7 per cent had used cannabis in the past 12 months. Slightly less than 10 per cent of them admitted to driving a car under the influence – eight times on average – during the 12-month period (Alrvarez et al 2007).

As regards drivers examined following a suspicion of being under the influence, a ten-year registration (1995-2004) was conducted in Sweden regarding the number and type of drug effects. Primarily due to the training and method development of

the police, the number of people discovered to be under the influence rose beginning in 1999 when a new law that entailed zero-tolerance for THC in the blood for prosecution purposed. The proportion of those taken into custody (with positive drug tests) who had THC in their blood remained around 30 per cent since 1999, but the absolute number has nearly quadrupled (Johns et al 2008).

Background factors among those who drive under the influence of cannabis

In the Spanish study described above, the following factors were found to have a connection with and affected the likelihood of driving under the influence of cannabis:

- size of the home town
- number of other drugs in the past year
- experience of cannabis-related problems (such as an absence from work or conflicts with the police), which entail that the person had problems of abuse or dependence (Alvarez et al 2007).

C. G. A. Jones et al recruited (by way of an advertisement) 320 abusers in Sidney. Through interviews, they identified who had driven a motor vehicle within an hour of smoking in the past year. These people constituted the study group, which was compared with the control group, the rest of the abusers, as regards potential predictors (factors that increase the likelihood) of "driving under the influence". The following conditions were found to be significantly over-represented in the study group:

- poly-drug abuse (as regards other drugs)
- the view that cannabis smoking did not increase the risk of accidents
- cannabis dependence
- early start of cannabis use – applied to women (Jones et al 2007).

If some cautious conclusions are to be drawn from these two studies and the study by Blows and colleagues referred to above, it would be that the following measures should be implemented to prevent harms in traffic caused by cannabis smoking:

1. offer treatment to large-scale consumers of cannabis
2. arrange information to all potential and active cannabis smokers regarding the risks of combining cannabis use/abuse with the operation of motor vehicles
3. provide information regarding current legislation

Part 4. Physical harm

17. Cannabis and pregnancy

Summary of Chapter 17

THC (see Chapter 2) is a substance which passes from the mother's blood system to that of the foetus, which means that THC can produce direct harmful effects on the foetus during pregnancy.

There is a risk that habitual cannabis abuse during pregnancy may affect the foetus, with resulting lower birth weight and shorter birth height.

As regards the risk of foetal damage in the proper sense, the risk of some rare forms of children's cancer has received considerable attention. It has since been shown that the smoking of cannabis plays a role in the formation of a type of cardiac anomalies, which are on the rise in the United States. That being said, it does seem that we can exclude the risk of malformations being caused by chromosomal damage produced by cannabis.

The most worrying scientific findings concern – not surprisingly – damage to the child's central nervous system. A very long-term Canadian study found that children of cannabis-smoking mothers had sustained damage to cognitive functions which did not become noticeable until the children reached the age of four. The reason for the late appearance of this damage is assumed to be that the functions involved are "executive" cognitive functions which are not taken into use until the child is four to six years old.

Another long-term study shows similar associations between exposure during the foetal stage and relatively late (at age 6 and 10, respectively) behavioural disturbances. The effect on intelligence has now also been able to be shown by these kinds of studies.

THC is a substance which passes from the mother's blood to that of the foetus. This means that THC can cause direct damage to the foetus during pregnancy. (THC is also passed on to the infant via breast-milk.) Animal experiments have shown a number of very serious effects on the gestation of, and on the young born to, females which have been given cannabis or THC during gestation. These findings have naturally given rise to questions concerning the risks to which the human foetus is exposed if the mother smokes hashish or marijuana during pregnancy (Abel, 1985).

Researchers are here confronted with the usual problems of finding a reliable design for their studies, including comparable control groups. Further, research of this type is faced with particular difficulties as regards finding means of excluding other factors that might explain damage that has been observed, such as other drugs (including alcohol and tobacco), inadequate nutrition and infections during pregnancy. Moreover, it is also difficult to find suitable methods of measurement with sufficient sensitivity to detect even damage of a subtle nature.

The conceivable – and suspected – harmful effects of cannabis can be divided into the following categories:

- effects on birth weight, birth height, etc. (similar to the effects of tobacco smoking during pregnancy)
- increased risk of malformation
- effects on the central nervous system of the foetus
- other effects on the foetus.

Effects on birth weight etc.

Until the mid-1980s, there were doubts as to the effects of cannabis on factors such as birth weight. Early studies produced varying results and were not always conducted with sufficient thoroughness. A series of later studies have shown that cannabis smoking during pregnancy is statistically associated with a lower average birth weight (Hatch & Bracken, 1986; Zuckerman et al., 1989) and a shorter average body height (Zuckerman et al., 1989; Tennes et al., 1985).

However, findings which in certain respects call into question the effect of both cocaine and marijuana on birth weight have been reported in a multi-centre study (Shiono et al., 1995). This study does not find any significant association between marijuana smoking during pregnancy and a lower birth weight of the child. If one looks solely at the association between mothers found to have marijuana in their blood during pregnancy and the birth weight of their children, though, there turns out to be a clear tendency which points in the same direction as the studies mentioned above. The overall picture is that – when account is taken of the quality of different studies, the methods they use to establish current abuse and the selection of pregnant women for the respective studies – *cannabis use, at least habitual cannabis use, during pregnancy represents a risk that the pregnancy and the foetus will be affected, with reduced birth weight and birth height as a consequence.*

The importance of these effects for the children's further development, however, is not known. The central result achieved is that it has been demonstrated that THC, by affecting the mother's hormonal system (and reducing the duration of pregnancy) or by its direct toxic action, produces such a clear and measurable effect on foetal development.

Increased risk of malformation

The term "malformation" here refers to abnormal anatomical developments of parts of the body and/or internal organs that are visible to the naked eye or can be detected by means of traditional examination methods used in radiology or laboratory diagnosis (to determine functional disturbance).

Previous research findings in this area are somewhat contradictory. While there are a few studies (e.g. Linn et al., 1983) which suggest a higher risk of malformation, most studies – and indeed the best-designed and best-executed ones – have produced findings which *contradict* the suspicion that the smoking of cannabis preparations increases the risk for malformation of parts of the body or of internal organs (Zuckerman et al., 1989).

Five years ago, I felt that the following line of thought was reasonable: Since there do exist studies which have arrived at a different conclusion, since the "exonerative" studies have certain methodological shortcomings, and since most of the "exonerative" studies relate to marijuana and were carried out during the first half of the 1980s or earlier when marijuana with low THC concentrations was still in widespread use, *it would be unwise to exclude cannabis as a cause of malformation until larger and better-controlled studies have been carried out* (Hall et al., 1994).

In 2004, L.J. Williams et al reported on an extensive study of the connection between ventricle septum defects (heart anomaly with an incomplete chamber wall) in newborns and the mothers' lifestyle, including as regards the smoking of marijuana. This study was in light of the fact that a significant increase in this malformation had been observed in the preceding 30 years in the United States. For cannabis-smoking mothers, the risk of having a child with a malformation was doubled. The risk increased with the intensity of the smoking.

Malformations due to cannabis-induced chromosome damage

Malformation can also be caused in other ways than through a direct toxic effect on the foetus. By damaging the genetic material of either parent, poisons capable of affecting the genes can cause malformation genetically. It has not been possible to prove that THC can produce such effects, and this risk has been dismissed in several reviews of research (Marijuana and Health, 1982; Hall et al., 1994).

Other effects on the foetus

Researchers have recorded several cases of rare cancers in children of mothers who smoked marijuana while pregnant or during the year before. In 1989, a tripling in the risk of acute non-lymphatic leukaemia was reported; in 1992, an increased risk of rhabdomyosarcoma was reported; and in 1993, an elevated risk of astrocytoma brain tumours was reported (Hall W. och Pacula R.L. 2003). In the United States, where these observations were made, no steady increase in these kinds of cancer has been reported in the general population in the years since.

Damage to the central nervous system of the foetus

It seems a reasonable suspicion that cognitive damage could arise at the foetal stage, bearing in mind the acute effects of cannabis on cognitive functions as well as the damage to cognitive functions caused in adults and young people by long-term exposure to cannabis (see Chapter 14). It is indeed within the area of effects on the central nervous system that the most disturbing scientific findings have been made.

A central position in this field of research is occupied by the Ottawa Prenatal Prospective Study (OPPS), carried out by a research team led by Peter Fried. This study of the children of mothers who smoked marijuana while pregnant is unique, particularly because of its long-term nature. The mothers were recruited to the research programme during the period 1978–1983. The children were examined from a neurological point of view immediately after birth and on several occasions during their first year; thereafter, they have been tested with regard to cognitive and psychomotor functions once a year up to the age of 16.

The researchers initially found signs of deficiencies in the children's neurological development, or signs of withdrawal effects. These symptoms disappeared during the first year, and when the children were examined with regard to motor development, perception and motor functions at the ages of one, two and three years, no deficiencies were found which could be related to their exposure to cannabis during the foetal stage. However, when the children were examined at the age of four, deficiencies were found in their memory and verbal ability. These deficiencies were no longer detectable at the ages of five and six – although the six-year-olds were found to have impaired ability to maintain attention. In the examinations at ages six to nine, several manifestations of deficiencies in cognitive functions were identified. The parents of the children who had been exposed to marijuana were also more likely to report behavioural disturbance in their children.

When the children were examined at ages nine to twelve, moderate functional impairment of a specific type was discovered: the children had reduced ability as regards *memory in connection with visual stimuli, analytical ability and integrative ability*. Moreover, *attention disturbances* were found. The same pattern recurred at ages 13–16 (Fried et al., 2003). It could be mentioned that the disturbances exhibited by children whose mothers had smoked cannabis while pregnant were different from the disturbances manifested by children whose mothers had smoked regular cigarettes only; the latter children were affected as regards overall intelligence and certain functions related to hearing.

To sum up, the research team found that – in addition to slight, transitory neurological deficiencies at birth – the children showed a slight disturbance to cognitive functions which was not detectable until they reached the age of four, and which subsequently disappeared. Other kinds of disturbance to cognitive functions, together with behavioural problems, appeared during the children's first school years and have proved possible to follow into the teenage years.

Fried (1995; 2003) presents a hypothesis as to why the deficiencies are not detectable until a few years after birth, which agrees well with the kinds of cognitive damage sustained by adults following long-term cannabis smoking: the damage caused at the foetal

stage is assumed not to become important until the child needs to function at a higher level with regard to "executive" functions (integrative cognitive functions of importance for processes such as problem-solving and planning). Cognitive disturbances of these kinds are among those also found in adults (Leavitt et al., 1994).

Most studies of the effects resulting from cannabis use during pregnancy do not follow the child beyond the age of one year. This is why there is only a very limited amount of scientific data either supporting the findings reported by Fried et al. or calling them into question. Day et al. (1993) found an association between marijuana smoking during pregnancy and lower intelligence-test scores at the age of three (but not before that age); this finding supports those of Fried. An association between marijuana smoking during pregnancy and sleeping problems in three-year-olds detected by Dahl (1995) also points in the same direction.

Peter Fried (1995) warns us against underestimating the risks to the foetus from cannabis exposure during pregnancy. He emphasises that his study looked at the effects arising from marijuana smoking at the end of the 1970s, reminding us that the marijuana in use today has a considerably higher THC content.

Recently, however, another long-term study has become available to us, even though the children included in it are five to six years younger. Goldschmidt et al. (2002) studied a group of just over 600 pregnant women, of whom slightly less than half smoked marijuana in different amounts while pregnant. Careful assessments of aspects such as the situation in the women's homes were carried out during the pregnancy and after they had given birth, in order to isolate the effects, if any, of cannabis. During the first years, the main emphasis was placed on reports from parents and, later, teachers. At the age of six, an association was found between exposure to marijuana and teacher reports of *delinquent-behaviour problems*.

When the children were ten years old, a more extensive assessment was carried out, including interviews with parents and teachers as well as standardised questionnaires. A clear association was found between exposure and *delinquency*. Further, it was found that these behavioural disturbances were mediated by pronounced hyperactivity, impulsiveness and deficiencies in attention. These characteristics proved to be associated with the degree of exposure to marijuana.

A comparison of these two long-term studies yields several similar tendencies. One of them is that test-score differences and behavioural disturbances, respectively, appear at a relatively late stage, as a manifestation of the fact that the damaged functions do not develop and start to be used until then. Further similarities include reports by parents and teachers, respectively, of disturbed/restless behaviour, which appear at more or less the same age. While Fried has focused more on measuring cognitive functions, Goldschmidt records behaviour.

In another cohort, tests have been conducted to determine if the aforementioned decrease in intellectual level observed in three-year-olds would also be observable in six-year-olds prior to beginning school. It was found that cannabis smoking during pregnancy can lower the intellectual level in six-year-old children (L. Goldschmidt et al 2008).

18. The effects of cannabis on the respiratory organs

Summary of Chapter 18

The most important of the known long-term harmful effects on the respiratory organs are chronic bronchitis and cancer of the respiratory tract.

There is a causal connection between long-term cannabis smoking and chronic bronchitis. Cannabis smoking on its own does not, however, increase the risk of full blown chronic obstructive pulmonary disease (COPD). The combination of cannabis and tobacco smoking, however, results in a synergic increase in the risk of COPD.

Cannabis smoke has a documented content of carcinogenic substances, and the discovery of preliminary stages of cancer in studies of large groups of cannabis smokers suggests that cannabis can cause cancer. These research findings, together with the numerous reports on the association between early onset of cancer in the upper respiratory tract and cannabis smoking, imply that the carcinogenic properties of cannabis smoke must be considered close to proven.

This chapter refers to a study that shows that cannabis smoking causes an elevated risk of lung cancer that is dependent on the total dose of cannabis.

A number of case studies and case-control studies show that cannabis smoking increases the risk of developing oral cancer, pharynx cancer and throat cancer in young people.

Bearing in mind the well-documented harmful effects of tobacco smoking on the human respiratory tract (above all chronic bronchitis, emphysema and cancer), researchers have long been interested in finding out whether cannabis smoke has similar or other effects on this system of organs. In this context, we can start by noting that cannabis is sometimes smoked mixed with tobacco, in which case the cannabis smoker is subject to the risks of harm associated with tobacco smoking. Further, there are many similarities between cannabis smoke and tobacco smoke, and so we could expect the side-effects to be similar (Gold, 1989). The main difference between the two is of course the presence of nicotine in tobacco and that of THC and other cannabinoids in cannabis.

In general, a tobacco smoker has more nicotine cigarettes a day than a cannabis smoker has cannabis cigarettes or pipefuls. On the other hand, cannabis is smoked – at least in the Western world – using an inhalation technique different from that commonly used by tobacco smokers who inhale. This technique, which ensures that "fuller use" is made of the cigarette or pipeful, consists of drawing the smoke deeper into the lungs and keeping it there for as long as possible. Furthermore, cannabis smokers tend to smoke as much of the cigarette as possible, while tobacco smokers often have filter-tips on their cigarettes and stub them out before it is absolutely necessary. This means that the amount of tar ingested by someone who smokes

cannabis at a dependence level for several years (i.e. several "joints" or pipefuls on a daily or near-daily basis) is very probably comparable with the amount ingested by a habitual tobacco smoker (Tennant, 1983).

Research findings concerning these expected harmful effects have to-date been limited compared with tobacco research. Possible explanations for this may be that:

- the harmful effects in question are side-effects which generally need decades before their development reaches a clinically observable level
- cannabis research is a young field compared with tobacco research.

Tobacco research is far ahead of cannabis research, both in time and quantity. The great breakthrough of tobacco research occurred in the first half of the 1960s, and the 1964 report by the American Surgeon General (the head of the US Public Health Service) was based on over 7,000 scientific reports, a number of which referred to longitudinal studies. It was possible to point to both a statistical association and a causal connection between smoking and a series of diseases, especially of the respiratory tract and the cardiovascular system. As early as at this stage, it was possible to show that smoking was the main cause of lung cancer in men, and the main cause of chronic bronchitis in both men and women. In 1989, 25 years later, the Surgeon General had access to more than 57,000 scientific works for the report published in that year. Cannabis research, on the other hand, was rather modest in scale in the early 1960s, and in 1996 the total number of scientific articles published on the subject probably still did not exceed 10,000. By 2003, tobacco research had yielded about 140,000 scientific works whereas the total body of cannabis research amounted to no more than roughly one-tenth of that number.

Clinical observations of how cannabis smoking increases the risk of acute infections of the nose, sinuses, pharynx and bronchi are common (Tennant, 1983).

The main long-term harmful effects on the respiratory (and adjacent) organs are: 1) *chronic bronchitis* (which may be followed by COPD, chronic obstructive pulmonary disease); and 2) *cancer of the respiratory tract, including mouth, pharynx and throat.*

Chronic bronchitis

Clinical experience of chronic bronchitis in young cannabis smokers is so common that doctors are advised always to suspect cannabis abuse when encountering bronchitis in *young* people.

Tashkin (1993) showed there to be a clear association between chronic bronchitis and regular, large-scale consumption of cannabis (3–4 "joints" daily over a period of at least five years).

Chronic bronchitis not rarely leads to COPD. Bloom et al. (1987) found that chronic marijuana smoking "had a striking effect on pulmonary symptoms and function". One manifestation of this effect on the lungs was that cannabis smok-

ers were significantly more likely to exhibit the kind of impaired lung function characteristic of the preliminary stages of COPD. This functional impairment was more pronounced in marijuana-smoking men than in comparable tobacco smokers. Doubt has been expressed, however, as to cannabis smokers developing COPD. W. C. Tan et al recently (2009) showed that cannabis along does not cause an elevated risk of developing COPD. However, the *combination* of cannabis and tobacco synergistically increases the risk of developing COPD.

Cancer of the lungs, bronchi, larynx, oral cavity, pharynx and oesophagus

Tashkin (1993) lists a series of factors which point towards cannabis smoking being associated with an increased risk of cancer of the respiratory tract:

- The tar found in cannabis smoke contains a 50 per cent larger amount of certain carcinogenic substances (among them the highly carcinogenic benzopyrene) than tobacco tar.
- The smoking of a marijuana cigarette produces four times as much tar as the smoking of a tobacco cigarette.
- Experiments on animals have shown that cannabis smoke or the tar from cannabis smoke has a carcinogenic effect.
- Large-scale consumers of cannabis exhibit a significantly higher frequency of cellular changes constituting a preliminary stage of cancer. This has been shown by e.g. Tennant (1983) and Tashkin (1993).
- There are several reported observations of groups of young patients exhibiting both cannabis abuse and cancer development. In these cases, the tumours have made their appearance 10–30 years earlier than in those patients whose cancer was caused solely by tobacco:

Of 887 patients with cancer of the upper or lower respiratory tract, Taylor (1988) found ten who were under 40 years old. Of these, five were large-scale consumers of cannabis, two smoked cannabis frequently but not daily, and one was probably a cannabis smoker. Two of them had cancer of the lungs, four had cancer of the larynx and four had cancer of the tongue.

In a retrospective review of patients with cancer of the throat and head at two centres in the United States, Endicott (1991) found 26 patients who were 41 years old or younger when their tumour was discovered. The average age of these patients was 32 (range: 17–41); the normal average age at which these cancers make their appearance is 57. All 26 patients were current or former marijuana smokers.

When examining the records of his patients with cancer of the head and throat over a 20-year period, Donald (1993) found 22 patients who had squamous-cell cancer and were 40 years old or younger when their tumour was discovered. Their average age was 26, and 19 of them were cannabis smokers, including 16 large-scale

consumers. In 13 of these 22 patients, the tumour was located on the tongue or elsewhere in the oral cavity. Only half of these patients were tobacco smokers as well.

Caplan et al. (1990), who reported two cases of tongue cancer in two marijuana smokers (who did not use alcohol or tobacco), proposed the hypothesis that cannabis may be responsible, as the sole factor, for tumours, especially in the upper respiratory tract.

Since Tashkin's review was made, further reports have been published. Sridhar et al. (1994) studied the connection between cannabis smoking and early onset of lung cancer. Of 110 patients with lung cancer, 13 were younger than 45 (range: 27–45); the average age of onset for lung cancer is 55 years or older. All of these 13 patients were cannabis smokers, compared with 6 per cent in the older group. Moreover, 12 of them were tobacco smokers as well.

In a review, Tashkin – who is the leading researcher in this field – looks again at the question of cancer and other risks to long-term cannabis smokers. In addition to the circumstances mentioned above, he presents further risk factors. First, he emphasises that examinations of the mucous membrane in long-term smokers suggest that THC weakens the immune defence against tumour cells. He goes on to account for five separate series of young men having developed cancer of the respiratory tract; all or a majority of the patients were cannabis smokers.

In a case-control study, a comparison had been made between 170 patients who had been diagnosed as having cancer and 170 matched control subjects without such a diagnosis. The proportion of cannabis smokers was clearly larger in the cancer group. The risk increased with the total amount of cannabis ingested by a person. The finding with the most serious implications was perhaps that those who had smoked both tobacco and cannabis ran a many times higher (36-fold) risk of developing cancer. There is reason to suspect that the combination of tobacco and cannabis leads not only to a summation effect, but also to a synergistic effect (Tashkin, et. al., 2002).

In a case-control study, S. Aldington et al. (2008) found that cannabis smokers had an elevated, total-dose-dependent risk of developing lung cancer. The study was based on lung cancer cases in patients under the age of 55. The cannabis smokers were divided into groups based on total dose expressed in "joint years" (equal to one joint/day for one year). Those with the highest volume – ten "joint years" – had a 5.7 times greater risk of developing lung cancer.

To conclude, there now exists a considerable body of documentation showing that cannabis smoke contains carcinogenic substances and probably has negative immunological effects. The discoveries of preliminary stages of cancer made in studies of large groups of cannabis smokers suggest that cannabis has carcinogenic effects. A number of case studies indicate this connection between cannabis smoking and early onset cancer of, above all, the upper respiratory tract. In a recent case-control study, it has been shown that cannabis smokers under the age of 55 have a total-dose-dependent elevated risk of developing lung cancer.

19. Cannabis and the cardiovascular system

Summary of Chapter 19

For people with coronary disease or hypertension, marijuana smoking constitutes an obvious risk. In other words, elderly people and people with a heart disease and/or high blood pressure have further reasons not to use cannabis.

Case presentations and reviews of two decades of case reports illustrate an entirely new picture as regards young people's (some under the age of 20) risk of developing acute cardiovascular disease in connection with cannabis smoking. They include a series of heart attacks (with six fatalities), 12 cases of stroke and four serious transient ischaemic attacks (TIA) (of which five under the age of 20). In addition, a greater number of the rare disorder, cannabis arteritis, have been reported.

Risks owing to acute effects

Cannabis intoxication initially causes palpitations of the heart and a certain drop in blood pressure; there is also often a phase characterised by a certain rise in blood pressure. These cardiovascular effects may contribute to provoking a state of anxiety, particularly in inexperienced smokers, but they were previously not otherwise considered to represent any risk to a young person with a healthy heart. Our knowledge of the cardiovascular complications to which cannabis can contribute is still limited, but during this decade in particular, researchers have produced scientific reports that provide a partially different picture than before.

> Damage to the ***heart*** (infarction, arrhythmia, etc.), ***blood vessels of the brain*** (stroke, TIA, etc.) and ***cannabis arteritis*** (blood vessels of the extremities, kidneys, etc.)

These are the target cardiovascular organs that are most affected. Although this is not a question of a large number of cases of illness on a multi-year basis, there are two factors that cause concern. On one hand, young people are involved, and on the other the number of reported cases is growing. The latter may nonetheless be an expression of both better diagnostics and more interest on the part of doctors and researchers. However, we cannot rule out that this phenomenon is an expression of it becoming more common among large-scale consumers and consumers of stronger preparations.

Heart: In a review of the English-language literature in 2005, 15 cases of infarction were found in the ages of 17-42. All of those who survived told of smoking cannabis, often at the time of the event, within an hour before it occurred or, in some cases, the same day. The six who were found dead had significant levels of THC in their blood (2-22 µg/litre) and in some cases THC in the urine. These infarction patients had no or extremely modest vascular changes, which could not, however, be considered as risk factors. *The assertion that one cannot die from the effects of cannabis may need to be re-evaluated.*

Korantzopolos et al (2007) summarise a review of reported cases of cannabis-induced cardiac fibrillation: Cardiac fibrillation should be incorporated into the physical illnesses that cannabis smoking can cause. The research group is of the opinion that every time a young person without predisposing factors for fibrillation develop this cardiac disorder, cannabis smoking should be considered as a cause.

M.A. Mittelman et al (2008) approached the problem of cannabis infarction in a different way. An average of four days after the infarction, 3,882 infarction patients were interviewed. With the interview, they established which of the patients had smoked cannabis in the past year. These 124 people were asked if they had smoked within 24 hours before the infarction and ultimately if they had smoked during the hour before. Through the use of *case-crossover design*, it was possible to then calculate the increased risk of infarction during the 60 minutes after smoking cannabis. After controls, the increase in risk was 4.8. From the large review above, we should keep in mind that those affected by infarction had often smoked within an hour before the infarction or had THC concentrations in the blood and possibly the urine that corresponded to recent cannabis consumption.

Stroke: The same review covers 12 reports which present 17 patients with cerebrovascular events in connection with cannabis smoking. Of these, 12 were cases of stroke proper and four were TIA. The patients were in the ages 15-32, of which five were under the age of 20 (D.G.E. Caldicott et al 2005).

One should keep in mind that this report presents a summary of multiple case studies. The apparently remarkable relationship between cardiovascular events and healthy young people who abuse cannabis has not been addressed in any true scientific work. The researchers David Caldicott and his co-workers also put forward a very tentative and humble line of thought as to the possible causal associations. "Are we witnessing an artefact due to an overlap of a very rare condition and a very widespread habit of cannabis smoking?", is one of their reflections. In their reasoning, they otherwise present interesting multi-dimensional explanatory models.

Cannabis arteritis: As early as the 1960s, an inflammatory arterial disease was described that appears in connection with generally long-term cannabis smoking. This conditions reminded one of a inflammatory arterial disease called endarteritis obliterans or Buerger's disease, which is relatively uncommon in Sweden. The latter has a relationship to tobacco that is similar to the relationship of "cannabis

arteritis" to cannabis. It is important to note that these are inflammatory diseases, in contrast to the more common arteriosclerotic conditions. These inflammatory conditions are treated in a different manner, and if they go untreated, they can lead to repeated local problems with pain, ulcers and possible amputation. We do not know why cannabis arteritis has lived such an obscure life for some time and is now receiving attention. The conditions has been uncommon, but probably underdiagnosed. One reason may of course be that, like the other cardiovascular diseases, it is becoming a more common companion of cannabis.

I. Peyrot et al (2007) provides a presentation of three new cases and a brief overview of the 25 cases that have been reported in the literature since the introduction of the syndrome in 1960 (*Les artérites du cannabis indica*, J. Sterne et G. Ducastaingt) together with the 26 first cases.

The 28 patients are 18-40 years old, of which one third have some vulnerability to coronary disease, such as high cholesterol, diabetes, etc. Most also smoke tobacco. All of the cases are from the 2000s, which indicates that the new-found interest in the disease is fairly current. It may possibly concern a true increase.

Risks owing to more long-term effects

Although we have, at present, no scientific proof that cannabis use causes cardiovascular diseases in the longer term, on closer inspection there are certain disturbing facts which should give us food for thought. We may, for example, recall what was said in Chapter 18 with regard to the difference in developmental level between the research into tobacco smoking and that into cannabis smoking;and also with regard to the different smoking techniques, where it was said that, because of the method used to smoke cannabis, the lungs of the smoker are exposed to four times as much tar from a cannabis cigarette as from a tobacco cigarette.

20. Cannabis and fertility

Summary of Chapter 20

Cannabis smoking disrupts the hormonal balance of both men and women. Research into the consequences that this effect may have on the fertility of men and women has yielded contradictory results. There does, however, remain a suspicion that cannabis smoking may lead, in both sexes, to a relative reduction of fertility, which is of importance above all in people who already have a tendency towards low fertility owing to other factors.

More than two decades ago, the suspicion arose that cannabis smoking might have a negative effect on the fertility of men. The researchers held that the hormonal effects (particularly a reduction in testosterone) suggested by gynaecomastia (enlarged breasts) ought to have a negative impact on sperm production. Subsequent animal experiments have pointed in the same direction, while direct studies of the sperm production of cannabis-smoking men have yielded contradictory results (Bloch, 1983). Both Hollister (1986) and Gold (1989) maintain that it is very uncertain what this effect on testosterone levels means in terms of sperm production. It is probably the case that these disturbances matter the most in teenagers and in men who already have a low level of sperm production owing to other factors.

The effect of cannabis on fertility in women is also uncertain. Research has shown disturbances to hormone secretion the effects of which include disruptions to the menstrual cycle. These findings, together with those from animal experiments, suggest that cannabis probably has a certain fertility-reducing effect which, as in the case of men, may be of importance above all in those cases where the individual already exhibits other tendencies towards reduced fertility (Gold, 1989).

More recent research does not appear to have provided greater clarity in these issues.

21. The effects of cannabis on the immune system

Summary of Chapter 21

Despite almost three decades of research, the question as to the effect of cannabis smoke on the human immune system must be considered to be unanswered.

The human immune system involves several organs or parts of organ systems. The immune system is of decisive importance for the body's defence against infection (bacteria, viruses and other micro-organisms) as well as against certain types of cancer. It is also involved in the development of allergies and auto-immune diseases.

In his review article Marijuana and Immunity, Hollister (1992) begins by saying that few areas of research are as filled with controversy as the question of the effect caused by marijuana on the immune system. He goes through the findings of studies carried out at the different levels where the various components of the immune system operate, and his conclusion is that the question of the effect caused by cannabinoids on the immune system remains unanswered after more than 15 years of research. Nobody has been able to call this conclusion into question in a convincing manner. Quite simply, we do not know what importance, if any, the changes observed have with regard to the body's defence against infection and the development of cancer.

Hollister also noted that the level of interest directed towards this area of research fell over the latter part of the 1980s. The probable explanation is that questions related to HIV occupied the attention of immunologists at the same time as the relationship of cannabis to the immune system appeared to be a less fruitful subject of research than it previously did. It can be added that this research seems to have gained momentum again in connection with different attempts to make medicinal use of cannabis.

Despite intensive study of the effects caused by cannabinoids on various aspects of the immune system, Klein et al. (1998) summed up the situation by saying that the questions put to researchers at the time still could not be answered.

It has now been established that cannabis has no immunologically negative effects on HIV/AIDS.

Otherwise, no decisive progress appears to have been made in this field of research.

22. Other physical disorders

Summary of Chapter 22

A research team has found a somewhat strong connection between cannabis smoking and testicular cancer. Continued studies will have to test the strength of this connection.

A connection between cannabis smoking and testicular cancer of the non-seminoma type has been observed (J. Daling et al 2009). While conducting a population-based case-control study, men with a certain variant of this type of cancer were found to have a 2.3 greater likelihood of being cannabis smokers. Additional studies are needed to further investigate a possible connection.

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Glossary

A

Amotivational syndrome	Certain personality traits caused by chronic cannabis abuse.
Anandamide	A substance similar to cannabinoids which occurs normally in the human body.
Anhedonia	The inability to feel joy or pleasure.
Antipsychotic	Having the quality of counteracting psychotic symptoms (usually said of medicinal drugs).
2-arachidonylglycerol	A substance similar to cannabinoids which occurs normally in the human body.
Atrioventricular block (AT block)	A serious disturbance to the conduction system of the heart.

B

Bronchitis	An inflammation or irritability of the mucous membrane of the bronchial tubes.

C

CAN	Swedish Council for Information on Alcohol and Other Drugs.
Cannabidiol (CBD)	A cannabinoid.
Cannabinoids	Substances contained in the cannabis plant.

Cannabis receptors — See *Receptors*. The cannabis receptors can be stimulated both by exogenous (not occurring naturally in the body) cannabinoids such as THC and by endogenous (occurring naturally in the body) cannabinoids such as anandamide.

Confounding factor — Co-variant factor. The scientific term for an interfering factor which, if not controlled for, may disturb the study of a relationship or connection.

Cerebral — Of or relating to the brain (cerebrum).

D

Delirium — An acute confusional state.

Depersonalisation syndrome — A mental disorder characterised by a profound sense of unreality as regards the surrounding world and/or oneself.

Dysphoria — A feeling of dissatisfaction and irritation.

E

Endocannabinoids — Substances similar to cannabinoids which occur normally in the human body.

Euphoria — A pronounced sense of well-being.

H

Cerebral atrophy — A shrivelling of the brain.

Cardiac arrhythmia — Irregular rhythm of the heart. If more than temporary, it is a manifestation of damage to the conduction system of the heart.

I

Interaction — Refers here to the mutual effects that two substances (such as a medicinal drug and a narcotic drug) have on each other, possibly with a negative outcome for the individual.

K

Cardiac — Of or relating to the heart.

Cognitive functions — Intellectual functions such as thought and memory.

Confusion — A profound state of bewilderment; disorientation.

L

Latent — The opposite of manifest. Refers to a predisposition towards an illness which has not broken out.

M

Manifest — The opposite of latent. Refers to a disease which has broken out.

Metabolite — A product of the body's processes for breaking down substances.

N

Neuroleptics — Medicinal drugs for the treatment of psychoses.

O

Opiates — Drugs (narcotic and medicinal) derived from the opium poppy.

Opioids	Opiates and synthetically produced narcotic and medicinal drugs which are closely related to the opiates.

P

Paroxysmal tachycardia	A suddenly occurring, rapid but regular heart rhythm.
Prepsychotic	Close to the breakout of psychotic illness.
Prospective study	A longitudinal, long-term, study which is started before the influencing factor whose effect is to be studied has started affecting the study group.
Psychoactive substances	Substances producing an effect on mental functions.
Psychomotor functions	The functions responsible for co-ordinating the brain and the locomotor system (the organs used to move the body: the skeleton, the muscles and the nerves).
Psychotoxic substances	Substances producing a noxious/toxic effect on mental functions (usually by affecting brain cells).

R

Randomisation	(Scientific term.) Random distribution of study subjects to a study group and a control group.
Receptors	Structures at the surface of nerve cells which receive signals from neurotransmitter substances (mainly secreted from other nerve cells). Together, the signals from thousands of receptors generate outgoing signals from the nerve cell.
Relapse	Recurrence.

S

Schizophreniform psychosis — A psychosis that is similar to schizophrenia, but does not meet all the criteria to be diagnosed as schizophrenia.

Suicide — The act of killing one's self.

Synergism — A situation where the joint effect of two or more factors is greater than the sum of the effects of the individual factors.

T

THC — Abbreviation for *delta-9-tetrahydrocannabinol*, which is the most psychoactive of the cannabinoids.

THC-COOH — A non-psychoactive metabolite of THC.

TIA — Abbreviation of *transient ischaemic attacks*. Short-lived, transient ischaemia in the brain.

Tolerance — A consequence of the development of dependence, meaning that the individual needs ever-higher doses to achieve the same effect.

V

Vulnerable — A person with an elevated sensitivity to a certain type of stress.

W

Withdrawal — Abbreviation of *withdrawal symptoms*. Discomfort felt as the supply of an addictive substance is broken off.

This report is a survey of the harmful effects – mental as well as physical – which can arise as a consequence of cannabis use.

The author, Jan Ramström, is a psychiatrist with several years' experience of specialised substance-abuse care. A long-time clinical department head in the field of general psychiatry, he has been affiliated with the Swedish National Board of Health and Welfare for nine years as a scientific advisor in issues of psychiatry and substance abuse. His previous publications include other reports as well as several textbooks in the fields of substance abuse, psychiatry and adolescent development.

This report is intended for healthcare providers, information officers and others in need of knowledge-based information on the consequences of cannabis use.

The report is a revised edition, the first edition of which was published in 1997 and the second in 2004.

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Swedish National Institute of **Public Health**

Swedish National
Institute of Public Health
Distribution Service
SE-120 88 Stockholm

fhi@strd.se
www.fhi.se

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